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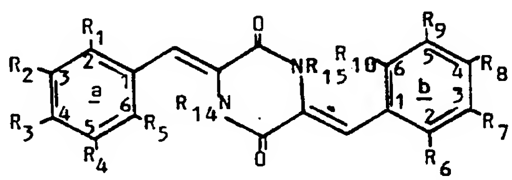


(A)

(57) Abstract

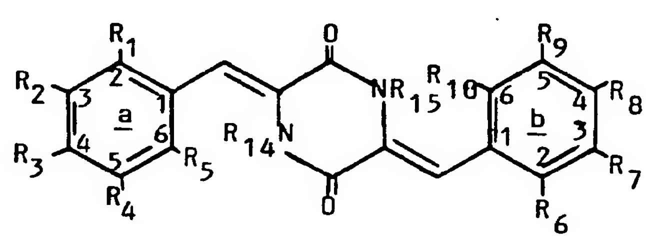
A diketopiperazine of formula (A) wherein each of R_{14} and R_{15}, which may be the same or different, is independently selected from hydrogen and C_1-C_6 alkyl provided at least one of R_{14} and R_{15} is C_1-C_6 alkyl; and R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more hydrogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11})R^{12}$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11}COR^{12})$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl or, when R^{11} and R^{12} are attached to the same nitrogen atom, they may alternatively form with the nitrogen atom a saturated five or six-membered ring; and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; and pharmaceutically acceptable salts and esters thereof; are modulators of multiple drug resistance.

Pharmaceutically active diketopiperazines

The present invention relates to compounds useful as modulators of multiple drug resistance (MDR), to their preparation and to pharmaceutical and veterinary compositions containing them.

The resistance of tumours to treatment with certain cytotoxic agents is an obstacle to the successful chemotherapeutic treatment of cancer patients. A tumour may acquire resistance to a cytotoxic agent used in a previous treatment. A tumour may also manifest intrinsic resistance, or cross-resistance, to a cytotoxic agent to which it has not previously been exposed, that agent being unrelated by structure or mechanism of action to any agent used in previous treatments of the tumour. These phenomena are referred to collectively as multiple drug resistance (MDR). Disadvantages of drugs which have so far been used to modulate MDR, termed resistance modifying agents or RMAs, are that they frequently possess a poor pharmacokinetic profile and/or are toxic at the concentrations required for MDR modulation.

It has now been found that a series of diketopiperazine derivatives have activity as modulators of multiple drug resistance. The present invention therefore provides the use of a diketopiperazine of formula (A):



(A)

wherein each of R_{14} and R_{15}, which may be the same or different, is independently selected from hydrogen and C_1-

C_6 alkyl provided at least one of R_{14} and R_{15} is C_1-C_6 alkyl; and each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, -cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl or, when R^{11} and R^{12} are attached to the same nitrogen atom, they may alternatively form with the nitrogen atom a saturated five or six membered heterocyclic ring; and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; in the manufacture of a medicament for use as a modulator of multiple drug resistance.

The numerals 1 to 10 denote ring positions on the phenyl groups in formula A. The letters a and b refer to the two phenyl rings themselves.

When any two adjacent groups of R_1 to R_{10} form, together with the carbon atoms to which they are attached, a benzene ring, that ring is either unsubstituted or it may be substituted by any of the options specified above for R_1 to R_{10}. The benzene ring forms, together with ring a or b respectively, an optionally substituted naphthalene ring structure.

When ring a or b is substituted phenyl, the benzene ring may be substituted at any of the ortho, meta and para positions by one or more substituents, for example one, two or three substituents, which may be the same or different,

independently selected from the groups specified above for R_1 to R_{10} other than hydrogen.

An alkyl group may be linear or branched, or may comprise a cycloalkyl group. A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl, tert-butyl or cyclopropylmethyl group. A halogen is, for example, fluorine, chlorine, bromine or iodine. A C_1-C_6 alkyl group substituted by halogen may be substituted by 1, 2 or 3 halogen atoms. It may be a perhaloalkyl group, for example trifluoromethyl.

A C_1-C_6 alkoxy group is typically a C_1-C_4 alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-butoxy, sec-butoxy or tert-butoxy group. A C_1-C_6 alkylthio group is typically a C_1-C_4 alkylthio group, for example methylthio, ethylthio, propylthio, i-propylthio, n-butylthio, sec-butylthio or tert-butylthio.

When R^{11} and R^{12} form a heterocyclic group together with the nitrogen atom to which they are attached, it is, for example, an N,N-tetramethylene group.

In compounds of formula A free rotation may occur at room temperature about the single bonds connecting rings a and b to the double bonds at positions 3 and 6 of the 2,5-piperazinedione ring. Positions 2 and 6, and positions 3 and 5, in both rings a and b can therefore be considered as equivalent. As a consequence the following pairs of substituents can be viewed as interchangeable: R_1 and R_5; R_2 and R_4; R_6 and R_{10}; and R_7 and R_9.

One of R_{14} and R_{15} is C_1-C_6 alkyl and the other is hydrogen or C_1-C_6 alkyl. When R_{14} and R_{15} are both C_1-C_6 alkyl they may be the same or different. Preferred C_1-C_6 alkyl groups for R_{14} and R_{15} are Me, Et and cyclopropylmethyl. For example R_{14} is C_1-C_6 alkyl and R_{15} is H or C_1-C_6 alkyl, or R_{15} is C_1-C_6 alkyl and R_{14} is H or C_1-C_6 alkyl. In one embodiment R_{14} is Me, Et or cyclopropylmethyl and R_{15} is H, Me, Et or cyclopropylmethyl. In a second embodiment R_{15} is Me, Et or

cyclopropylmethyl and R_{14} is H, Me, Et or cyclopropylmethyl.

Preferably one of rings a and b is unsubstituted or is mono-substituted whilst the other ring is unsubstituted or is substituted at one or more of positions 2 to 6. The ring which is mono-substituted may carry the substituent at any one of positions 2 to 6, for instance position 3 or 4, especially position 4. Thus for instance, when ring b is mono-substituted, one of R_6 to R_{10} is other than hydrogen, preferably R_7 or R_8, especially R_8. When ring a is mono-substituted, one of R_1 to R_5 is other than hydrogen, preferably R_2 or R_3, especially R_3. When one of rings a and b is mono-substituted the substituent R_1 to R_5, or R_6 to R_{10} respectively, is preferably selected from a halogen, for instance fluorine; an alkoxy group, for instance OMe; and an acetamido group -NHAc in which Ac denotes acetyl.

When one of rings a and b is unsubstituted, or is mono-substituted as described in the above paragraph, the other ring may bear any desired substitution pattern. For instance, the other ring may be unsubstituted or may be mono-, di- or tri-substituted at any of positions 2 to 6.

The said other ring may, for instance, be mono-substituted at any of positions 2 to 6. It may also be 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5- disubstituted, or 2,3,4-, 2,3,5-, 2,3,6- or 3,4,5-trisubstituted. Thus, when the said other ring is a and is mono-substituted, four of R_1 to R_5 are hydrogen and one is other than hydrogen. When the said other ring is ring a and is disubstituted, three of R_1 to R_5 are hydrogen and two are other than hydrogen. For example R_1 and R_2, or R_1 and R_3, or R_1 and R_4, or R_1 and R_5, or R_2 and R_3, or R_2 and R_4 are other than hydrogen whilst, in each case, the other three of R_1 to R_5 are hydrogen.

When the said other ring is ring a and is trisubstituted, two of R_1 to R_5 are hydrogen and three are other than hydrogen. For example, R_1, R_2 and R_3, or R_1, R_2 and R_4, or R_1, R_2 and R_5, or R_2, R_3 and R_4 are other than

hydrogen whilst, in each case, the other two of R_1 to R_5 are hydrogen.

When the said ring is b and is mono-substituted, four of R_6 to R_{10} are hydrogen and one is other than hydrogen. When the said other ring is b and is di-substituted, three of R_6 to R_{10} are hydrogen and two are other than hydrogen. For example R_6 and R_7, or R_6 and R_8, or R_6 and R_9, or R_6 and R_{10}, or R_7 and R_8, or R_7 and R_9, are other than hydrogen whilst, in each case, the other three of R_6 to R_{10} are hydrogen. When the said other ring is b and is trisubstituted, two of R_6 to R_{10} are hydrogen and three are other than hydrogen. For example R_6, R_7 and R_8, or R_6, R_7 and R_9, or R_6, R_7 and R_{10}, or R_7, R_8 and R_9 are other than hydrogen whilst, in each case, the other two of R_6 to R_{10} are hydrogen.

Alternatively, any two adjacent substituents in the said other ring may, together with the carbon atoms to which they are attached, complete a second benzene ring which is optionally substituted, thus forming an optionally substituted naphthyl group with the said other ring. For instance, in ring a R_1 and R_2, or R_2 and R_3 may form together with carbon atoms 2 and 3, or 3 and 4 respectively, an optionally substituted benzene ring which, in turn, forms with ring a a naphthyl group which is unsubstituted or substituted by one or more groups specified above for R_1 to R_{10}. In ring b R_6 and R_7, or R_7 and R_8 may form, together with carbon atoms 2 and 3 or 3 and 4 respectively, an optionally substituted benzene ring which, in turn, forms with ring b a naphthyl group which is unsubstituted or substituted by one or more groups specified above for R_1 to R_{10}. Typically the naphthyl group in either case is unsubstituted or is monosubstituted at position 1,2,3 or 4 of the naphthalene ring structure, especially position 4. For example R_1 and R_2 together with ring a, or R_6 and R_7 with ring b, form a 4-dimethylamino-1-naphthyl group.

In a preferred series of compounds of formula A each

of R_6 to R_{10} is hydrogen. In another preferred series of compounds, one of R_6 to R_{10} is selected from hydroxy, alkoxy, $NHCOR^{11}$, $-CO_2R^{11}$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, NO_2, $-SO_2N(R^{11}R^{12})$, $-SOR^{13}$, $-N(R^{11})COR^{12}$ and halogen and the other four of R_6 to R_{10} are H. Alkoxy may be, for instance, OMe or OBu^n. $NHCOR^{11}$ is typically -NHAc. CO_2R^{11} is typically -COOH or -COOMe. $N(R^{11}R^{12})$ is typically NMe_2 or N,N-tetramethylene. CON $(R^{11}R^{12})$ may be $-CONH_2$. SO_2R^{13} is typically SO_2Me, $SO_2N(R^{11}R^{12})$ is for example $-SO_2NMe_2$. SOR^{13} may be SOMe and $-N(R^{11})COR^{12}$ may be -$NMeCOBu^t$. Halogen is typically F or Cl. Preferably R_8 is alkoxy, especially OMe or OBu^n; $NHCOR^{11}$, especially -NHAc; $-CO_2R^{11}$, especially $-CO_2H$ or $-CO_2Me$; $-CON(R^{11}R^{12})$ especially $-CONH_2$; NO_2; $N(R^{11}R^{12})$ especially NMe_2 or N,N-tetramethylene; $-SOR^{13}$ especially -SOMe; $-SO_2N(R^{11}R^{12})$ especially $-SO_2NMe_2$ or halogen, especially F or Cl; and each of R_6, R_7, R_9 and R_{10} is H.

In the above-mentioned series of preferred compounds R_1 to R_5 are all hydrogen, or one or two of R_1 to R_5 are other than hydrogen whilst the others are hydrogen. For instance one of R_1, R_2 and R_3 is other than hydrogen. Alternatively R_1 and R_3, or R_2 and R_3, are other than hydrogen. Preferred values for the one or two of R_1 to R_5 which is or are other than hydrogen include alkoxy such as OMe or OBu^n, halogen such as Cl or F, hydroxy, $-N(R^{11}R^{12})$, $-CO_2R^{11}$, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$, $-NHCOR^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCOCH_2OR^{11}$, $-NHCOCH_2OCOR^{13}$, $-CH_2NHCOOR^{13}$ and CF_3. It is also preferred for R_1 and R_2, R_2 and R_3, R_3 and R_4 or R_4 and R_5 to form, together with the carbon atoms to which they are attached, a benzene ring.

Particularly preferred compounds are those wherein R_6, R_7, R_9 and R_9 are each H, R_8 is selected from H, OMe -NHAc, $-CO_2H$, $-CO_2Me$, $-COHN_2$, NO_2, $-NMe_2$, N,N-tetramethylene, SO_2Me, -SOMe and $-SO_2NMe_2$ and each of R_1 to R_5 is as specified above. In these preferred compounds R^1 to R^5 are preferably each independently selected from H, halogen,

hydroxy, C_1-C_6 alkoxy, nitro, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$, $-CO_2R^{11}$, $-OCOR^{13}$, CF_3, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOR^{11}$, $-N(R^{11}R^{12})$, $-NHCO(CH_2)_nOCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$ and $-CH_2NHCO_2R^{13}$ or R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_5, form with the carbon atoms to which they are attached an optionally substituted benzene ring. Still more preferably, R_1 and R_2 are independently H, nitro or halogen, R_3 is H, hydroxy, $-O(CH_2)_nN(R^{11}R^{12})$, $-OCOR^{13}$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, C_1-C_6 alkoxy, $-NHCO(CH_2)_nOR^{11}$, $-NHCO(CH_2)OCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, $-CH_2SR^{11}$ or $-NHCOR^{11}$; R_4 is H, halogen, C_1-C_6 alkoxy, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$ or $-CO_2R^{11}$; and R_5 is H, nitro or halogen; or R_2 and R_3, R_3 and R_4 or R_4 and R_5 form, together with the carbon atoms to which they are attached, an optionally substituted benzene ring.

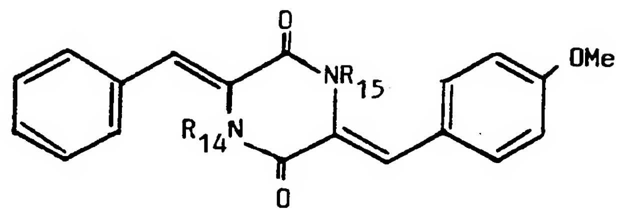
In one embodiment R^8 is NHAc, each of R_6, R_7, R_9 and R_{10} is H; R_1 is H or halogen such as Cl or F; R_2 is H, R_3 is halogen such as F or Cl, C_1-C_6 alkoxy such as OMe, $-N(R^{11}R^{12})$ such as NMe_2 or $-NHCOOR^{13}$ such as $-NHCOOBu^t$; R_4 is H and R_5 is halogen such as F, Cl, Br, or is CF_3.

In a second embodiment R^8 is OMe, each of R_6, R_7, R_9 and R_{10} is H; R^1 is H, nitro or halogen such as Cl; R^2 is H; R^3 is H, hydroxy, $-OCOR^{13}$ such as OAc, $-NHCO(CH_2)_nOCOR^{11}$ such as $-NHCOCH_2OAc$ or $-NHCOCH_2OR^{11}$ such as $-NHCOCH_2OH$; R_4 is H and R_5 is H or halogen such as F or Cl; or R_2 and R_3 form a benzene ring together with the carbon atoms to which they are attached.

In a third embodiment each of R_1, R_6, R_7, R_8, R_9 and R_{10} is H; R_2 is H, $-CH_2SCOR^{13}$ such as $-CH_2SAc$ or $-CH_2SR^{11}$ such as $-CH_2SH$; R_3 is $-CH_2SR^{11}$ such as $-CH_2SMe$, $-CH_2SCOR^{13}$ such as $-CH_2SAc$, $-NHCO(CH_2)_nCO_2R^{11}$ such as $-NHCO(CH_2)_3CO_2Me$, $-O(CH_2)_nCO_2R^{11}$ such as $-O(CH_2)_4CO_2H$, $-O(CH_2)N(R^{11}R^{12})$ such as $-O(CH_2)_3NMe_2$, or $-N(R^{11}R^{12})$ such as $-NMe_2$; and R_4 and R_5 are both H or both form, together with the carbon atoms to which they are attached, a benzene ring.

In one embodiment of the invention the compound of

formula A has the following formula (Aa):



(Aa)

wherein each of R_{14} and R_{15}, which may be the same or different, is independently H or CH_3 provided at least one is CH_3.

Certain diketopiperazines have been disclosed as having utility as bioactive agents. Yokoi et al in J. Antibiotics vol XLI No. 4, pp 494-501 (1988) describe structure-cytotoxicity relationship studies on a series of diketopiperazines related to neihumicin, a compound obtained from the micro-organism Micromonospora neihuensis. Kamei et al in J. Antibiotics vol XLIII No. 8, 1018-1020 disclose that two diketopiperazines, designated piperafizines A and B, have utility as potentiators of the cytotoxicity of vincristine.

General formula A embraces diketopiperazines which are novel. Accordingly, the present invention provides a diketopiperazine of formula (A) as defined above, or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of R_1 to R_{10} is H; and

(ii) R_{14} and R_{15} are both Me, R_8 is OMe and the rest of R_1 to R_{10} are H.

Examples of specific compounds of the invention are as follows. The compound numbering is adhered to in the rest of the specification:

(3Z,6Z)-3-benzylidene-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 1);

(3Z,6Z)-6-benzylidene-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 121);

(3Z,6Z)-3,6-dibenzylidene-1-methyl-2,5-piperazinedione (compound 122);

4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzoic acid, methyl ester (compound 124);
4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzoic acid (compound 125);
(3Z,6Z)-3-(3-hydroxymethylbenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione (compound 126);
(3Z,6Z)-3-benzylidene-1-methyl-6-(4-nitrobenzylidene)-2,5-piperazinedione (compound 127);
N,N-tetramethylene-4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzamide (compound 128);
(3Z,6Z)-6-(4-aminobenzylidene)-3-benzylidene-1-methyl-2,5-piperazinedione (compound 129);
((3Z,6Z)-3-Benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzamide (compound 130);
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 131);
(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 132);
(3Z,6Z)-6-(4-Methoxybenzylidene)-1-methyl-3-(2-nitrobenzylidene)-2,5-piperazinedione (compound 133);
(3Z,6Z)-6-(4-Methoxybenzylidene)-1-methyl-3-(4-N-methylacetamidobenzylidene)-2,5-piperazinedione (compound 134);
(3Z,6Z)-6-(2,6-Dichlorobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 135);
(3Z,6Z)-3-(4-Methoxybenzylidene)-1-methyl-6-(2-nitrobenzylidene)-2,5-piperazinedione (compound 136);
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 137);
(3Z,6Z)-3-(4-(3-N,N-Dimethylaminopropoxy)benzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione, hydrochloride (compound 138)
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-

trifluoromethylbenzylidene)-2,5-piperazinedione (compound 139)

(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(1-naphthylmethylene)-2,5-piperazinedione (compound 140)

(3Z,6Z)-6-Benzylidene-3-(4-dimethylaminobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 141);

(3Z,6Z)-6-Benzylidene-3-(2-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 142);

(3Z,6Z)-3-(4-Aminobenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione (compound 143);

(3Z,6Z)-6-Benzylidene-3-(2-fluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 144)

(3Z,6Z)-6-Benzylidene-3-(4-fluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 145)

(3Z,6Z)-6-Benzylidene-3-(2,4-difluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 146)

(3Z,6Z)-3-(4-Acetoxymethylbenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione (compound 147)

(3Z,6Z)-3-(3-Acetoxymethylbenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione (compound 148)

(3Z,6Z)-6-Benzylidene-3-(4-ethoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 149)

(3Z,6Z)-3,6-Dibenzylidene-1,4-dimethyl-2,5-piperazinedione (compound 150)

(3Z,6Z)-6-Benzylidene-3-(2,6-dichlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 151);

(3Z,6Z)-6-(4-aminobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (compound 152);

(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-N-methylacetamidobenzylidene)-2,5-piperazinedione (compound 153)

(3Z,6Z)-6-Benzylidene-3-(3,4-dichlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 154)

(3Z,6Z)-6-Benzylidene-3-(3-chlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 155)

(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-methylsulfinylbenzylidene)-2,5-piperazinedione (compound

156)

N,N-Dimethyl-4-((3Z,6Z)-6-Benzylidene-1,4-dimethyl-2,5-dioxopiperazin-3-ylidene)methylbenzenesulfonamide (compound 157)

(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(2-N-methyltrimethylacetamidobenzylidene)-2,5-piperazinedione (compound 158)

(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-phenylbenzylidene)-2,5-piperazinedione (compound 159)

4-((3Z,6Z)-6-Benzylidene-1,4-dimethyl-2,5-dioxopiperazin-3-ylidene)methylbenzoic acid, methyl ester (compound 160)

(3Z,6Z)-6-Benzylidene-3-(4-bromobenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 161)

(3Z,6Z)-3-(2,4-Difluorobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 162)

(3Z,6Z)-3-(4-Bromobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 163)

(3Z,6Z)-3-(4-Fluorobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (compound 164)

(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-1,4-dimethyl-6-(2-nitrobenzylidene)-2,5-piperazinedione (compound 165)

(3Z,6Z)-6-Benzylidene-1-cyclopropylmethyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (compound 166)

(3Z,6Z)-3-Benzylidene-1-cyclopropylmethyl-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 167)

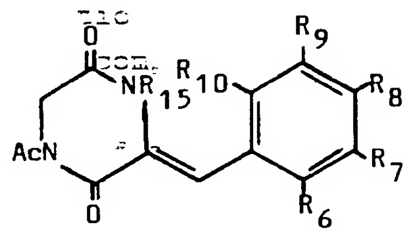
(3Z,6Z)-6-Benzylidene-1-cyclopropylmethyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (compound 168)

(3Z,6Z)-3,6-Dibenzylidene-1-ethyl-4-methyl-2,5-piperazinedione (compound 169)

(3Z,6Z)-3-Benzylidene-1-cyclopropylmethyl-6-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (compound 170)

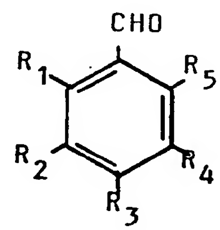
Compounds of formula A, both known and novel, may be prepared by a process which comprises either (i) condensing compound of formula (I)

prepared by a process which comprises either (i) condensing compound of formula (I)



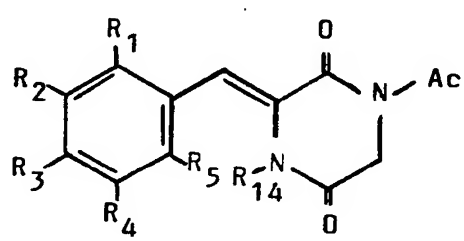
(I)

wherein R_6 to R_{10} and R_{15} are as defined above and are optionally protected, with a compound of formula (II):



(II)

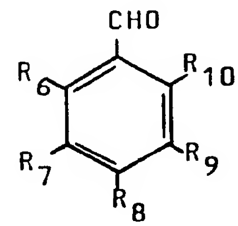
wherein R_1 to R_5 are defined above and are optionally protected, in the presence of a base in an organic solvent, thereby obtaining a compound of formula A in which R_{14} is hydrogen; or (ii) condensing a compound of formula (I'):



(I')

wherein R_1 to R_5 and R_{14} are as defined above and are

optionally protected, with a compound of formula (III):



(III)

wherein R_6 to R_{10} are as defined above and are optionally protected, in the presence of a base in an organic solvent, thereby obtaining a compound of formula A in which R_{15} is hydrogen; and, in either case (i) or (ii), if desired, converting the resulting compound of formula A in which R_{14} or R_{15}, respectively, is hydrogen into a corresponding compound of formula A in which R_{14} and R_{15}, respectively, is a C_1-C_6 alkyl group, by treatment with an alkylating agent; and/or if required, removing optionally present protecting groups and/or, if desired, converting one compound of formula A into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or, if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers of compounds of formula A into the single isomers.

A compound of formula A produced directly by the condensation reaction between (I) and (II) or (I') and (III) may be modified, if desired, by converting one or more of groups R_1 to R_{10} into different groups R_1 to R_{10}. These optional conversions may be carried out by methods known in themselves. For example, a compound of formula A in which one or more of R_1 to R_{10} is an ester group may be converted to a compound of formula A wherein the corresponding substituent is a free -COOH group, by acid or alkaline hydrolysis at a suitable temperature, for example from ambient temperature to 100°C.

A compound of formula A in which one or more of R_1 to R_{10} is a $-CO_2H$ group may be converted into a compound of formula A wherein the corresponding substituent is esterified by esterification, for example by treating the carboxylic acid with a suitable C_1-C_6 alkyl alcohol in the presence of 1,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which one or more of R_1 to R_{10} is a free $-CO_2H$ group may be converted into a compound of formula A in which the corresponding substituent is a group $-CON(R^{11}R^{12})$, wherein R^{11} and R^{12} are as defined above, for example by treatment with ammonia or an amine in the presence of 1,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which one or more of R_1 to R_{10} is a free $-CO_2H$ group may be converted into a compound of formula A wherein the corresponding substituent is a $-CH_2OH$ group by reduction, for example using borane in a suitable solvent such as tetrahydrofuran.

A compound of formula A in which one or more of R_1 to R_{10} is a nitro group may be converted into a compound of formula A in which the corresponding substituent is an amino group by reduction under standard conditions, for example by catalytic hydrogenation.

Protecting groups for R_1 to R_{10} in any of the compounds of formulae (I), (I'), (II) and (III) are optionally introduced prior to step (i) or step (ii) when any of groups R_1 to R_{10} are groups which are sensitive to the condensation reaction conditions or incompatible with the condensation reaction, for example a -COOH, $-CH_2OH$ or amino group. The protecting groups are then removed at the end of the process. Any conventional protecting group suitable for the group R_1 to R_{10} in question may be employed, and may be introduced and subsequently removed by well-known standard methods.

The condensation reaction between compounds (I) and (II) or (I') and (III) is suitably performed in the

presence of a base which is potassium t-butoxide, sodium hydride, potassium carbonate, sodium carbonate, caesium carbonate, sodium acetate, potassium fluoride on alumina, or triethylamine in a solvent such as dimethylformamide, or in the presence of potassium t-butoxide in t-butanol or a mixture of t-butanol and dimethylformamide. The reaction is typically performed at a temperature from 0°C to the reflux temperature of the solvent.

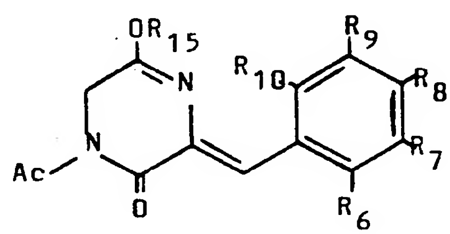
The alkylation of a compound of formula A wherein R_{14} or R_{15} is H is carried out using an appropriate conventional alkylating agent such as a haloalkane, for example an iodoalkane, or a dialkylsulphate, in the presence of a base in an organic solvent. The base may be, for example, sodium hydride, sodium carbonate or potassium carbonate. A suitable solvent is then DMF. Another suitable base is aqueous sodium hydroxide, in which case a suitable cosolvent is, for example, dioxan, THF or DMF.

The compounds of formula (I) may be prepared by a process comprising reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (III) as defined above, in the presence of a base in an organic solvent, thereby obtaining a compound of formula (I) wherein R_{15} is hydrogen; and, if desired, treating the resulting compound of formula (I) with an alkylating agent to obtain a compound of formula (I) in which R_{15} is a C_1-C_6 alkyl group. Similarly, the compounds of formula (I') may be prepared by a process which comprises reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (II) as defined above, in the presence of a base in an organic solvent, thereby obtaining a compound of formula (I') in which R_{14} is hydrogen; and, if desired, treating the resulting compound of formula (I') with an alkylating agent to obtain a compound of formula (I') in which R_{14} is a C_1-C_6 alkyl group.

If necessary, the resulting compound of formula (I) or (I') can be separated from other reaction products by chromatography.

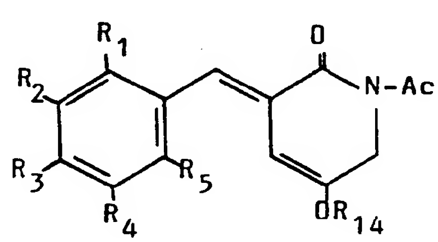
The reaction of 1,4-diacetyl-2,5-piperazinedione with the compound of formula (III) or (II) is suitably performed under the same conditions as described above for the condensation between compounds (I) and (II), or (I') and (III).

The alkylation of a compound of formula (I) in which R_{15} is hydrogen, or a compound of formula (I') in which R_{14} is hydrogen, is suitably carried out using the same conventional alkylating agents and under the same conditions as described above for the alkylation of compounds of formula (A) in which R_{14} is hydrogen. The alkylation step in the case of a compound (I) where R_{15} is hydrogen typically gives rise to a mixture of the compound of formula (I) in which R_{15} is a C_1-C_6 alkyl group and its isomer of the following formula (IV) in which R_{15} is a C_1-C_6 alkyl group:



(IV)

The alkylation step in the case of a compound (I') where R_{14} is hydrogen typically gives rise to a mixture of the compound of formula (I') where R_{14} is a C_1-C_6 alkyl group and its isomer of formula (IV') where R_{14} is a C_1-C_6 alkyl group:



(IV')

The mixture of compounds (I) and (IV), where R_{15} is other than hydrogen, or compounds (I') and (IV'), where R_{14} is other than hydrogen, can readily be separated by chromatography, for example on silica gel. Suitable eluants include ethyl acetate and hexane, or methanol and dichloromethane.

The substituted benzaldehydes of formulae (II) and (III) are known compounds or can be prepared from readily available starting materials by conventional methods. The 1,4-diacetyl-2,5-piperazinedione used as a starting material in the preparation of compounds of formula (I) may be prepared by treating 2,5-piperazinedione (glycine anhydride) with an acetylating agent. The acetylation may be performed using any conventional acetylating agent, for example acetic anhydride under reflux or, alternatively, acetic anhydride at a temperature below reflux in the presence of 4-dimethylaminopyridine.

Compounds of formula (I) wherein R_{15} is H may also be prepared by the microwave irradiation of a mixture comprising 1,4-diacetyl-2,5-piperazinedione, a compound of formula (III) and potassium fluoride on alumina (as base) in the absence of solvent.

Compounds of formula (I) wherein R_{15} is H may alternatively be prepared directly from 2,5-piperazinedione (glycine anhydride) by a process which comprises treating the 2,5-piperazinedione with a mixture comprising a compound of formula (III), sodium acetate and acetic anhydride at an elevated temperature, for example under reflux.

Compounds of formula (I') wherein R_{14} is H may be prepared by analogous processes, replacing compound (III) in each case by a compound of formula (II).

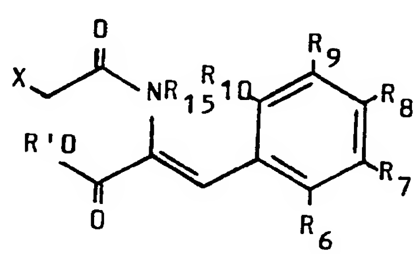
Compounds of formula A may also be prepared by a process comprising the microwave irradiation of (i) a mixture comprising a compound of formula (I) as defined above wherein R_{15} is H or C_1-C_6 alkyl, a compound of formula (II) and potassium fluoride on alumina, or (ii) a mixture

comprising a compound of formula (I') wherein R_{14} is H or C_1-C_6 alkyl a compound of formula (III) and potassium fluoride on alumina, or (iii) a mixture comprising 1,4-diacetylpiperazine-2,5-dione, a compound of formula (II), a compound of formula (III) and potassium fluoride on alumina. The irradiation is performed in the absence of a solvent. The resulting compound in which R_{14} and R_{15} are both H may then be alkylated using an appropriate alkylating agent, for example as described above.

Compounds of formula A may also be obtained directly by a process which comprises condensing together 1,4-diacetyl-2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of a base in an organic solvent. Suitable bases, solvents and reaction conditions are as described above for the condensation reaction between, for example, compounds (I) and (II).

An alternative direct process for the preparation of compounds of formula A comprises condensing together 2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of sodium acetate and acetic anhydride at elevated temperature, for example under reflux.

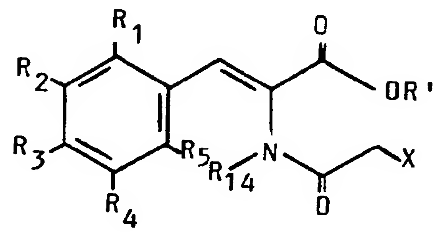
An alternative process for the preparation of compounds of formula (I) comprises treating a compound of formula (V):



(V)

wherein R_6 to R_{10} are as defined above, X is a halogen and R' is a C_1-C_6 alkyl group, with ammonia followed by acetic anhydride.

Compounds of formula (I′) may be prepared by an analogous process which comprises treating a compound of formula (V′):



(V′)

wherein R_1 to R_5, X and R^1 are as defined above, with ammonia followed by acetic anhydride.

X in formula (V) or (V′) is typically iodine. R′ is, for example, a C_1-C_4 alkyl group such as a methyl, ethyl, propyl, i-propyl, butyl, sec-butyl or tert-butyl group.

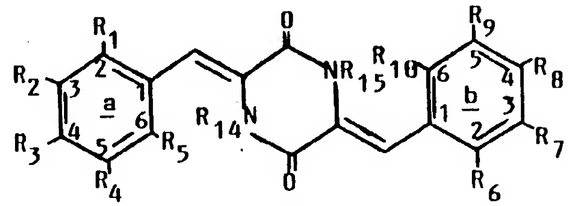
A review of synthetic approaches to unsaturated 3-monosubstituted and 3,6-disubstituted-2,5-piperazinediones is provided in <u>Heterocycles</u>, 1983, <u>20</u>, 1407 (C.Shin).

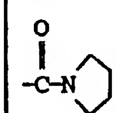
Compounds of formula (A) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods. Suitable salts include salts with pharmaceutically acceptable, inorganic or organic, bases. Examples of inorganic bases include ammonia and carbonates, hydroxides and hydrogen carbonates of group I and group II metals such as sodium, potassium, magnesium and calcium. Examples of organic bases include aliphatic and aromatic amines such as methylamine, triethylamine, benzylamine, dibenzylamine or α-or β-phenylethylamine, and heterocyclic bases such as piperidine, 1-methylpiperidine and morpholine.

Compounds of formula (A) may also be converted into pharmaceutically acceptable esters. Suitable esters include branched or unbranched, saturated or unsaturated C_1-C_6 alkyl esters, for example methyl, ethyl and vinyl esters.

Preferred compounds of formula A are depicted by means of their substitution patterns and identified by compound number in Table 1 which follows. Characterising data for the compounds are set out in Table 5 in Example 16. Diketopiperazine derivatives which are N-unsubstituted in the piperazine ring and can be converted by alkylation into compounds of formula A are depicted by substitution pattern in Table 2.

TABLE 1



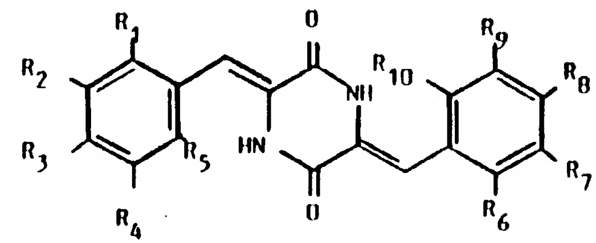
COMPOUND NO.	R_{14}	R_{15}	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
121	Me	H	H	H	H	H	H	H	H	OMe	H	H
122	Me	H	H	H	H	H	H	H	H	H	H	H
123	H	Me	H	H	H	H	H	H	H	OH	H	H
124	H	Me	H	H	H	H	H	H	H	CO_2Me	H	H
125	H	Me	H	H	H	H	H	H	H	CO_2H	H	H
126	Me	Me	H	H	H	H	H	H	CH_2OH	H	H	H
127	H	Me	H	H	H	H	H	H	H	NO_2	H	H
128	H	Me	H	H	H	H	H	H	H		H	H
129	H	Me	H	H	H	H	H	H	H	NH_2	H	H
130	H	Me	H	H	H	H	H	H	H	$CONH_2$	H	H
131	H	Me	H	H	NHAc	H	H	H	H	OMe	H	H

COMPOUND NO.	R_{14}	R_{15}	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
132	H	Me	Cl	H	H	H	Cl	H	H	OMe	H	H
133	H	Me	NO_2	H	H	H	H	H	H	OMe	H	H
134	H	Me	H	H	NMeAc	H	H	H	H	OMe	H	H
135	Me	H	Cl	H	H	H	Cl	H	H	OMe	H	H
136	Me	H	NO_2	H	H	H	H	H	H	OMe	H	H
137	H	Me	H	H	OMe	H	H	H	H	NHAc	H	H
138	H	Me	$-O(CH_2)_3NMe_2HCl$	H	H	H	H	H	H	OMe	H	H
139	Me	Me	H	H	H	H	H	H	H	CF_3	H	H
140	Me	Me	H	H	H	H	H	- benzene -		H	H	H
141	Me	Me	H	H	H	H	H	H	H	NMe_2	H	H
142	Me	Me	H	H	H	H	H	OMe	H	H	H	H
143	Me	Me	H	H	H	H	H	H	H	NH_2	H	H
144	Me	Me	F	H	H	H	H	H	H	H	H	H
145	Me	Me	H	H	F	H	H	H	H	H	H	H
146	Me	Me	F	H	F	H	H	H	H	H	H	H
147	Me	Me	H	H	H	H	H	H	H	CH_2OAc	H	H
148	Me	Me	H	H	H	H	H	H	CH_2OAc	H	H	H
149	Me	Me	H	H	H	H	H	H	H	OEt	H	H
150	Me	Me	H	H	H	H	H	H	H	H	H	H

COMPOUND NO.	R_{14}	R_{15}	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
151	Me	Me	H	H	H	H	H	Cl	H	H	H	Cl
152	H	Me	H	H	OMe	H	H	H	H	NH_2	H	H
153	Me	Me	H	H	H	H	H	H	H	NMeAc	H	H
154	Me	Me	H	H	H	H	H	H	Cl	Cl	H	H
155	Me	Me	H	H	H	H	H	H	Cl	H	H	H
156	Me	Me	H	H	H	H	H	H	H	SOMe	H	H
157	Me	Me	H	H	H	H	H	H	H	SO_2NMe_2	H	H
158	Me	Me	H	H	H	H	H	$NMeCOBu^t$	H	H	H	H
159	Me	Me	H	H	H	H	H	H	H	Ph	H	H
160	Me	Me	H	H	H	H	H	H	H	CO_2Me	H	H
161	Me	Me	H	H	Br	H	H	H	H	H	H	H
162	Me	Me	H	H	OMe	H	H	F	H	F	H	H
163	Me	Me	H	H	OMe	H	H	H	H	Br	H	H
164	Me	Me	H	H	OMe	H	H	H	H	F	H	H
165	Me	Me	Cl	H	H	H	Cl	NO_2	H	H	H	H
166	H	$-CH_2-$◁	H	H	OMe	H	H	H	H	H	H	H
167	H	$-CH_2-$◁	H	H	H	H	H	H	H	OMe	H	H
168	Me	$-CH_2-$◁	H	H	OMe	H	H	H	H	H	H	H
169	Me	Et	H	H	H	H	H	H	H	H	H	H

COMPOUND NO.	R_{14}	R_{15}	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
170	Me	$-CH_2-\triangleleft$	H	H	H	H	H	H	H	OMe	H	H
171	H	Me	H	H	OMe	H	H	H	H	NO_2	H	H

TABLE 2



COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN REF EXAMPLE
21	Cl	H	H	H	Cl	H	H	H	H	H	5
22	H	H	H	H	H	H	H	H	H	H	10
23	H	H	OAc	H	H	H	H	H	H	H	6
24	H	NO_2	H	H	H	H	H	H	H	H	6
25	H	H	OEt	H	H	H	H	H	H	H	5
26	H	H	NHAc	H	H	H	H	OMe	H	H	7
27	H	- Benzene -		H	H	H	H	OMe	H	H	14
28	NO_2	H	H	H	H	H	H	OMe	H	H	8
29	Cl	H	H	H	Cl	H	H	OMe	H	H	7
30	H	H	NH_2	H	H	H	H	H	H	H	13
31	H	OAc	H	H	H	H	H	H	H	H	6
32	OAc	H	H	H	H	H	H	H	H	H	6

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN REF EXAMPLE
33	H	OH	H	H	H	H	H	H	H	H	13
34	H	H	NHAc	H	H	H	H	H	H	H	5
35	H	NO_2	H	H	H	H	NO_2	H	H	H	11
36	H	H	OH	H	H	H	H	OMe	H	H	13
37	H	H	OAc	H	H	H	H	OMe	H	H	7
38	NHAc	H	H	H	H	H	H	H	H	H	5
39	NH_2	H	H	H	H	H	H	H	H	H	13
40	H	H	NHAc	H	H	Cl	H	H	H	Cl	9
41	H	H	NMeAc	H	H	H	H	OMe	H	H	7
42	H	H	Cl	H	H	H	H	NHAc	H	H	9
43	H	H	CH_2OAc	H	H	H	H	H	H	H	5
44	H	H	CH_2NHAc	H	H	H	H	H	H	H	5
45	H	H	H	H	H	H	H	H	H	H	5
46	H	H	SO_2Me	H	H	H	H	OMe	H	H	7
47	H	H	OBu^n	H	H	H	H	OMe	H	H	7
48	H	H	OBu^n	H	H	H	H	H	H	H	5
49	H	H	OPr^i	H	H	H	H	OMe	H	H	7
50	H	H	Bu^t	H	H	H	H	OMe	H	H	7
51	H	H	Bu^t	H	H	H	H	H	H	H	5

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
52	H	H	OPr^i	H	H	H	H	H	H	H	5
53	Br	H	H	H	H	H	H	OMe	H	H	7
54	F	H	F	H	H	H	H	H	H	H	5
55	Br	H	H	H	H	H	H	H	H	H	5
56	H	H	CH_2NHBOC	H	H	H	H	OMe	H	H	7
57	H	H	OMe	H	H	H	H	CH_2SMe	H	H	7
58	H	H	NHAc	H	H	H	H	CH_2OAc	H	H	9
59	H	H	H	H	H	H	H	CH_2SMe	H	H	5
60	H	H	OMe	H	H	H	H	CH_2SO_2Me	H	H	7
61	H	CH_2SAc	H	H	H	H	H	H	H	H	5
62	H	CO_2Me	H	H	H	H	H	H	H	H	5
63	H	CH_2SAc	H	H	H	H	H	OMe	H	H	7
64	H	CH_2SH	H	H	H	H	H	H	H	H	13
65	NO_2	H	H	H	H	H	H	H	H	H	6
66	H	H	CH_2NHBOC	H	H	H	H	H	H	H	5
67	H	H	CH_2NH_2	H	H	H	H	OMe	H	H	13
68	H	H	CH_2NHBOC	H	H	H	H	NHAc	H	H	9
69	F	H	F	H	H	H	H	OMe	H	H	7
70	CF_3	H	H	H	H	H	H	OMe	H	H	7

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
71	F	H	H	H	H	H	H	NHAc	H	H	9
72	H	H	F	H	H	H	H	NHAc	H	H	9
73	OMe	H	OMe	H	H	H	H	OMe	H	H	7
74	H	H	NO_2	H	H	H	H	H	H	H	6
75	H	H	H	H	H	H	H	$O(CH_2)_3NMe_2$	H	H	5
76	H	H	H	H	H	H	H	CH_2SAc	H	H	5
77	F	H	F	H	H	H	H	NHAc	H	H	9
78	CF_3	H	H	H	H	H	H	NHAc	H	H	9
79	Br	H	H	H	H	H	H	NHAc	H	H	9
80	H	H	OMe	H	H	H	H	$CONH_2$	H	H	7
81	H	H	OMe	H	H	H	H	$OCOBu^t$	H	H	7
82	H	H	NHAc	H	H	H	H	$OCOBu^t$	H	H	9
83	H	H	NHCOOMe	H	H	H	H	OMe	H	H	7
84	Cl	H	OH	H	H	H	H	OMe	H	H	7
85	Cl	H	OH	H	H	H	H	H	H	H	5
86	H	H	NHAc	H	H	H	H	NMe_2	H	H	12
87	H	H	$NHCOCH_2OAc$	H	H	H	H	OMe	H	H	7
88	H	H	$NHCOCH_2OH$	H	H	H	H	OMe	H	H	13
89	H	H	H	H	H	-Benzene-		NMe_2	H	H	5

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
90	H	OMe	OMe	H	H	H	H	H	H	H	5
91	H	OMe	OMe	H	H	H	H	OMe	H	H	7
92	H	OMe	OMe	H	H	H	H	NHAc	H	H	9
93	H	H	OCH_2CO_2Me	H	H	H	H	H	H	H	5
94	H	H	$CH_2NHCO(CH_2)_3CO_2Me$	H	H	H	H	H	H	H	5
95	H	H	$CH_2NHCO(CH_2)_4CO_2Et$	H	H	H	H	H	H	H	5
96	H	H	$O(CH_2)_4CO_2Me$	H	H	H	H	H	H	H	5
97	H	H	$O(CH_2)_4CO_2H$	H	H	H	H	H	H	H	13
98	H	H	$O(CH_2)_3NMe_2.HCl$	H	H	H	H	H	H	H	15
99	H	H	$O(CH_2)_2NMe_2.HCl$	H	H	H	H	H	H	H	15
100	H	H	$CH_2NHCO(CH_2)_3CO_2Me$	H	H	H	H	OMe	H	H	7
101	H	H	OCH_2CO_2H	H	H	H	H	H	H	H	13
102	H	H	$O(CH_2)_2NMe_2$	H	H	H	H	H	H	H	5
103	F	H	H	H	H	H	H	OMe	H	H	7
104	H	H	CH_2OH	H	H	H	H	NHAc	H	H	13
105	H	H	H	H	H	H	H	CN	H	H	6

Cancer cells which exhibit multiple drug resistance, referred to as MDR cells, display a reduction in intracellular drug accumulation compared with the corresponding drug-sensitive cells. Studies using in vitro derived MDR cell lines have shown that MDR is often associated with increased expression of a plasma membrane glycoprotein (P-gp) which has drug binding properties. P-gp is thought to function as an efflux pump for many hydrophobic compounds, and transfection studies using cloned P-gp have shown that its overexpression can confer the MDR phenotype on cells: see, for example, Ann. Rev. Biochem 58 137-171 (1989).

A major function of P-gp in normal tissues is to export intracellular toxins from the cell. There is evidence to suggest that overexpression of P-gp may play a clinical role in multiple drug resistance. Increased levels of P-gp mRNA or protein have been detected in many forms of human cancers - leukaemias, lymphomas, sarcomas and carcinomas. Indeed, in some cases P-gp levels have been found to increase in tumour biopsies obtained after relapse from chemotherapy.

Inhibition of P-gp function in P-gp mediated MDR has been shown to lead to a net accumulation of anti-cancer agent in the cells. For example, Verapamil a known calcium channel blocker was shown to sensitise MDR cells to vinca alkaloids in vitro and in vivo: Cancer Res., 41, 1967-1972 (1981). The proposed mechanism of action involves competition with the anti-cancer agent for binding to the P-gp. A range of structurally unrelated resistance-modifying agents acting by this mechanism have been described such as tamoxifen (Nolvadex:ICI) and related compounds, and cyclosporin A and derivatives.

Compounds of formula A, both novel and known, and their pharmaceutically acceptable salts and esters (hereinafter referred to as "the present compounds") have been found in biological tests to have activity in modulating multiple drug resistance. The results are set

out in Example 15 which follows. The present compounds may therefore be used as multiple drug resistance modifying agents, also termed resistance-modifying agents, or RMAs. The present compounds can modulate, e.g. reduce, or eliminate multiple drug resistance. The present compounds can therefore be used in a method of potentiating the cytotoxicity of an agent which is cytotoxic to a tumour cell. Such a method comprises, for instance, administering one of the present compounds to the tumour cell whilst the tumour cell is exposed to the cytotoxic agent in question. The therapeutic effect of a chemotherapeutic, or antineoplastic, agent may thus be enhanced. The multiple drug resistance of a tumour cell to a cytotoxic agent during chemotherapy may be reduced or eliminated.

A human or animal patient harbouring a tumour may be treated for resistance to a chemotherapeutic agent by a method comprising the administration thereto of one of the present compounds. The present compound is administered in an amount effective to potentiate the cytotoxicity of the said chemotherapeutic agent. Examples of chemotherapeutic or antineoplastic agents which are preferred in the context of the present invention include vinca alkaloids such as vincristine and vinblastine; anthracycline antibiotics such as daunorubicin and doxorubicin; mitoxantrone; actinomycin D and plicamycin.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to

10 mg/kg, most commonly in the range of 0.01 to 5 mg/kg, body weight. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

A diketopiperazine of formula (A) or a pharmaceutically acceptable salt or ester thereof is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceutically or veterinarily suitable form. An agent for use as a modulator of multiple drug resistance comprising any one of the present compounds is therefore provided.

For example, the solid oral forms may contain, together with the active compound, diluents such as lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose, or polyvinyl pyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs, sweeteners; wetting agents such as lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tabletting, sugar coating, or film-coating processes.

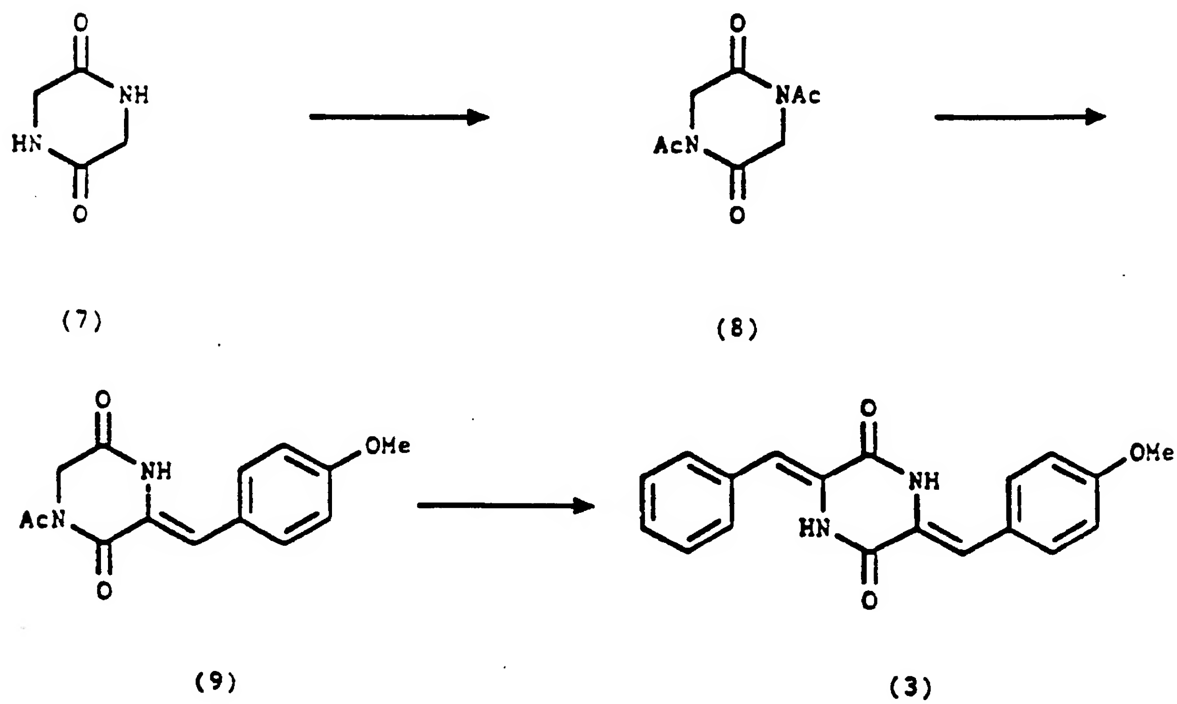
Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. In particular, a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate,

pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier such as sterile water, olive oil, ethyl oleate, glycols such as propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. Some of the present compounds are insoluble in water. A compound may be encapsulated within liposomes.

The following Examples illustrate the invention:

Reference Example 1: Preparation of (3Z,6Z)-6-Benzylidene-3-(4-methoxybenzylidene)-2,5-piperazinedione (3) (scheme 1)



(7) (8) (9) (3)

1,4-Diacetyl-2,5-piperazinedione (8)

1,4-Diacetyl-2,5-piperazinedione (8) was prepared by the published procedure (S.M. Marcuccio and J.A. Elix,

Aust. J. Chem., 1984, 37, 1791).

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9)

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) was prepared by the published procedure (T. Yokoi, L-M. Yang, T. Yokoi, R-Y. Wu, and K-H. Lee, J. Antibiot., 1988, 41, 494).

(3Z,6Z)-6-Benzylidene-3-(4-methoxybenzylidene)-2,5-piperazinedione (3)

A mixture of (3Z)-1-acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) (1.0g, 3.6 mmol), benzaldehyde (430 μl, 4.2 mmol) and triethylamine (1.14 ml), 8.2 mmol), in dry DMF (20 ml), was heated at 130°C for 18h. The reaction mixture was cooled to room temperature and poured into ethyl acetate (100 ml). A yellow solid precipitated which was filtered off and dried. Yield 360 mg (31%).

$C_{19}H_{16}N_2O_3$

^1H nmr (400 MHz d_6-DMSO):

δ: 3.80 (3H, s, O-Me); 6.77 (1H, s, CH=C); 6.78 (1H, s, CH=C); 6.98 (2H, d, J=8Hz, 2xC-H on Ar-OMe); 7.30-7.56 (7H, m, Ph and 2xC-H on Ar-OMe); 10.15 (2H, br.s, N-H).

^{13}C nmr (100 MHz d_6-DMSO)

δ: 58.68; 117.66; 118.03; 118.77; 128.11; 128.92; 129.95; 131.53; 132.11; 132.69; 134.44; 136.59; 161.39; 161.62; 162.71.

ms (desorption chemical ionisation, ammonia):

m/z (% relative intensity) : 321 (100) MH^+.

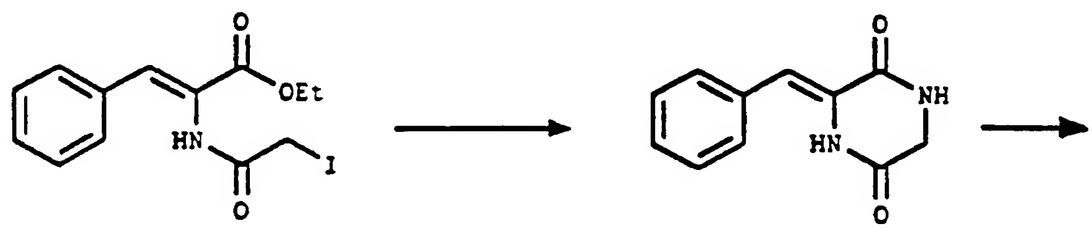
ir : KBr (diffuse reflectance):

v max (cm^{-1}) : 1620, 1700, 3100, 3220.

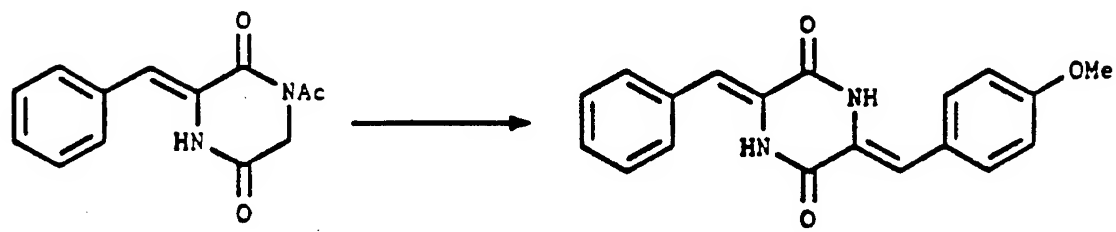
Elemental analysis:

Calculated for $C_{19}H_{16}N_2O_3$:	C 71.24, H 5.03, N 8.74.
Found:	C 70.92, H 5.02, N 8.80.
	C 70.89, H 5.06, N 8.79%

Reference Example 2: Preparation of (3Z,6Z)-6-Benzylidene-3-(4-methoxybenzylidene)-2,5-piperazinedione (3)(scheme 2)



(16) (17)



(18) (3)

Compound 16 is treated with ammonia and subsequently with acetic anhydride to yield 1-acetyl-3-benzylidene-2,5-piperazinedione (18).

Compound 18 is then condensed, in the presence of caesium carbonate or triethylamine in DMF, with 4-methoxybenzaldehyde to yield compound 3.

Reference Example 3: Preparation of 1-acetyl-3-benzylidene-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione (25.0g, 126 mmol), which is compound (8) mentioned in Reference Example 1, was heated at 120-130°C in DMF (200 ml) with triethylamine (17.6 ml, 126 mmol) and benzaldehyde (13.0 ml, 126 mmol).

After 4 h the mixture was cooled to room temperature and poured into EtOAc (1000 ml), and washed three times with brine. Any solid formed at this stage was filtered off. The filtrate was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was recrystallised from EtOAc:Hexane to give 11.78 g (38%) of the title compound as a yellow solid.

^1H NMR ($CDCl_3$ 400 MHz) δ=2.69 (3H, s) 4.54 (2H, s) 7.20 (1H, s) 7.40 (3H, m), 7.48 (2H, m), 7.93 (1H, br.s)

MS(DCI,NH_3): 262 (MNH_4^+, 20%), 245 (MH^+, 53%), 220 (52%), 204 (100%), 203 (100%)

Microanalysis	C	H	N
Calc	63.93	4.95	11.47
Found	64.11	5.02	11.41
	64.05	4.90	11.44

Reference Example 4: **Preparation of 1-acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione**

1,4-Diacetyl-2,5-piperazinedione (10.0g, 50 mmol), prepared by the published procedure mentioned in Reference Example 1, was stirred in DMF (40 ml) with 4-acetamidobenzaldehyde (8.24 g, 50 mmol) and triethylamine (7 ml, 50 mmol) and heated to 120°C. After 2½ h the mixture was cooled to room temperature, diluted with EtOAc (100 ml) and stirred overnight. The solid formed was collected, washed with EtOAc and dried to give 8.46 g (56%) of a yellow solid.

^1H NMR ($CDCl_3$+CF_3CO_2H, 400 MHz) δ=2.32 (3H, s) 2.72 (3H, s) 4.68 (2H, s) 7.36 (1H, s) 7.45 (2H, d, J=8Hz) 7.60 (2H, d, J=8Hz)

Microanalysis	C	H	N
Calc	59.80	5.02	13.95
Found	60.08	5.09	13.89

	60.11	5.07	13.86

Reference Example 5: Preparation of compound 96

1-Acetyl-3-benzylidene-2,5-piperazinedione (one equivalent), prepared according to Reference Example 3, was treated with 5-(4-formylphenoxy)pentanoic acid, methyl ester in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-8 hours. The title compound was obtained in 39% yield.

By the same method, but replacing 5-(4-formylphenoxy)pentanoic acid, methyl ester (which is benzaldehyde substituted at position 4 by $-O(CH_2)_4CO_2Me$) by the appropriately substituted benzaldehyde, the following compounds were prepared:

Compound	Yield (%)	Compound	Yield (%)
21	66	25	37
34	56	89	37
38	84	89	68
44	44	45	91
48	69	51	68
52	72	54	69
55	73	59	50
61	44	62	63
66	15	75	49
76	60	45	15
89	37	90	74
93	69	94	39
95	26	96	39
102	45		

Reference Example 6: Preparation of Compound 31

1-Acetyl-3-benzylidene-2,5-piperazinedione (one equivalent), prepared according to Reference Example 1, was treated with 3-acetoxybenzaldehyde (one equivalent) in the

presence of triethylamine (1-2 equivalents) in DMF at 130°C for 2-6 hours. The title compound was obtained in 61% yield.

By the same method, but replacing 3-acetoxybenzaldehyde by the appropriately substituted benzaldehyde, the following compounds were prepared:

Compound	Yield (%)
23	16
24	43
32	41
65	27
74	77
105	50

Reference Example 7: Preparation of compound 103

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1 equivalent), which is compound (9) mentioned in Reference Example 1, was treated with 2-fluorobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 69% yield.

By the same method, but replacing the 2-fluorobenzaldehyde by the appropriately substituted benzaldehyde with the exception of compound 84 which was prepared by condensation with 4-acetoxy-2-chlorobenzaldehyde, the following compounds were prepared:

Compound	Yield (%)
26	80
29	70
37	21
41	34
46	16

Compound	Yield (%)
63	71
69	20
70	10
73	38
80	45

47	46	81	5
49	60	83	41
50	56	84	Low
53	77	87	33
57	49	91	74
60	71	100	20
		103	69

Reference Example 8: Preparation of compound 28

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1 equivalent), compound (9) in Reference Example 1, was treated with 2-nitrobenzaldehyde (1 equivalent) and triethylamine (1-2 equivalents) and DMF at 130°C for 2-6 hours. The title compound was obtained in 45% yield.

Reference Example 9: Preparation of Compound 77

1-Acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione (1 equivalent), prepared according to Reference Example 4, was treated with 2,4-difluorobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 60% yield.

By the same method, but replacing 2,4-difluorobenzaldehyde by the appropriately substituted benzaldehyde, the following compounds were obtained:

Compound	Yield (%)	Compound	Yield (%)
42	50	40	40
68	26	58	22
72	41	71	36
79	11	78	16
92	68	82	16

Reference Example 10: Preparation of compound 22

1,4-Diacetyl-2,5-piperazinedione (1 equivalent), prepared by the published procedure mentioned in Reference

Example 1, was treated with benzaldehyde (2.1 equivalents) in the presence of triethylamine (2.5 equivalents) in DMF at 130°C for 8 hours. The title compound was obtained in 89% yield.

Reference Example 11: Preparation of compound 35

1,4-Diacetyl-2,5-piperazinedione (1 equivalent), prepared by the published procedure mentioned in Reference Example 1, was treated with 3-nitrobenzaldehyde (1 equivalent) in the presence of triethylamine (1 equivalent) in DMF at room temperature for 18-20 hrs. The title compound was obtained in 9% yield together with 1-acetyl-3-(3-nitrobenzylidene)-2,5-piperazinedione (66% yield).

Reference Example 11a: Preparation of 1-acetyl-3-(4-dimethylaminobenzylidine)-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione, (1 equivalent), prepared as described in Reference Example 1, was treated with 4-dimethylaminobenzaldehyde (1 equivalent) in the presence of Et_3N in DMF at 130°C for 24 hrs. The title compound was obtained in 18% yield

Reference Example 12: Preparation of Compound 86

1-Acetyl-3-(4-dimethylaminobenzylidene)-2,5-piperazinedione (1 equivalent) as described in Reference Example 11a was reacted with 4-acetamidobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1 equivalent) in DMF at 80°C for 2-6 hours. The title compound was obtained in 56% yield.

Reference Example 13: Interconversions of Reference compounds

(i) Compound 31, prepared as described in Reference Example 6, was treated with aqueous lithium hydroxide in a mixture of MeOH and THF at room temperature for 2-3 hrs to give compound 33 in 91% yield.

(ii) Compound 61, prepared as described in Reference Example 5, was treated with aqueous lithium hydroxide in a mixture of MeOH and THF at room temperature for 3 hours to give compound 64 in 57% yield.

(iii) Compound 96, prepared as described in Reference Example 5, was treated with aqueous sodium hydroxide in THF at room temperature for 4 hours to give compound 97 in 54% yield.

(iv) Compound 37, prepared as described in Reference Example 7, was treated with aqueous sodium hydroxide in THF at room temperature for 8 hrs to give compound 36 in 30% yield.

(v) Compound 56, prepared as described in Reference Example 7, was treated with trifluoroacetic acid in CH_2Cl_2 at room temperature for 12 hrs to give compound 67 in 96% yield.

(vi) Compound 87, prepared as described in Reference Example 7, was treated with aqueous sodium hydroxide in THF at room temperature for 4 hours to give compound 88 in 69% yield.

(vii) Compound 65, prepared as described in Reference Example 6 was hydrogenated over 10% palladium on carbon as catalyst in CH_2Cl_2 in the presence of a few drops of trifluoroacetic acid to give compound 39 in 38% yield. Under the same conditions of hydrogenation compound 74 was converted into compound 30 in 95% yield.

(viii) Compound 93, prepared as described in Reference Example 5, was hydrolysed by treatment with aqueous sodium hydroxide in a mixture of MeOH and THF at room temperature for 18 hours to give compound 101 in 72% yield.

(ix) Compound 58, prepared as described in Example 9, was hydrolysed by treatment with aqueous sodium hydroxide in THF at room temperature for 3 hours to give compound 104 in 90% yield.

Reference Example 14: Preparation of Compound 27

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1

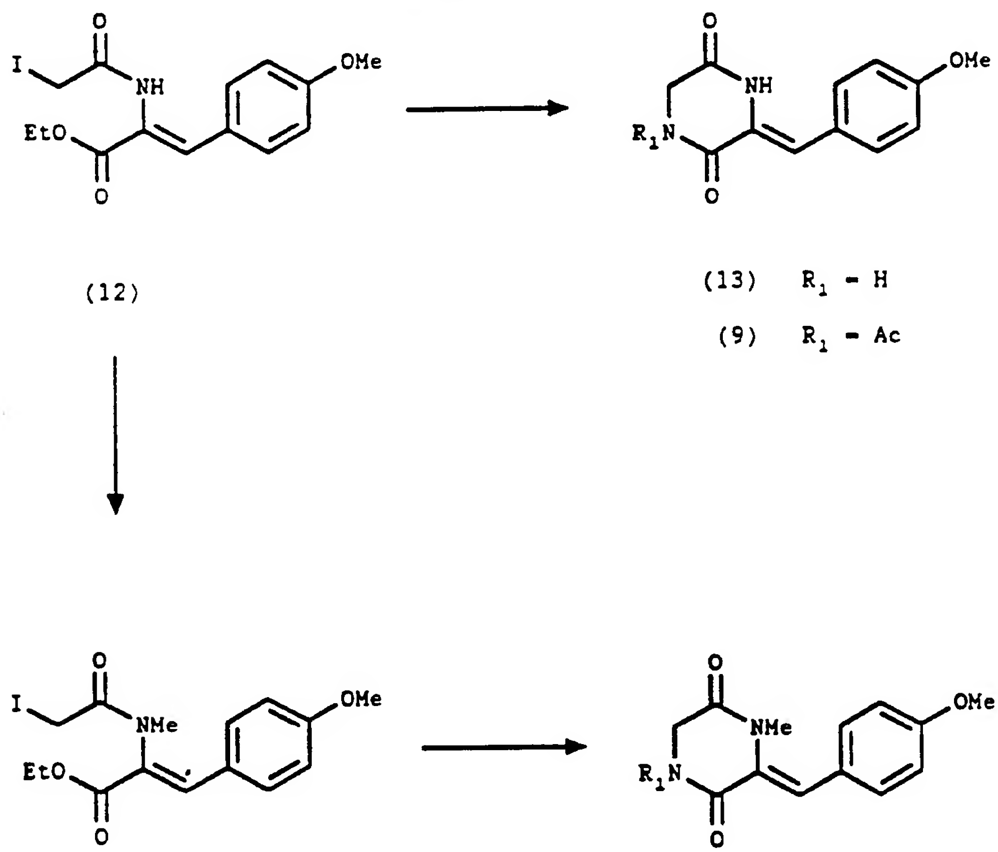
equivalent), compound (9) in Reference Example 1, was treated with 2-naphthaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1.0-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 84% yield.

Reference Example 15: Preparation of Salts

Compound 98, the hydrochloride salt of compound 102, was prepared by treatment of a solution of compound 102 in THF with 2 molar hydrochloric acid followed by sonication until a clear solution was obtained. The solvent was then removed *in vacuo* and the residual solution was freeze-dried to give compound 98.

Compound 99 was prepared by bubbling HCl gas through a solution of the corresponding free base in THF, followed by evaporation to dryness.

Reference Example 16: Preparation of (3Z)-1-acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) and 1-acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10) (Scheme 3)



(12)

(13) R_1 = H

(9) R_1 = Ac

(14)

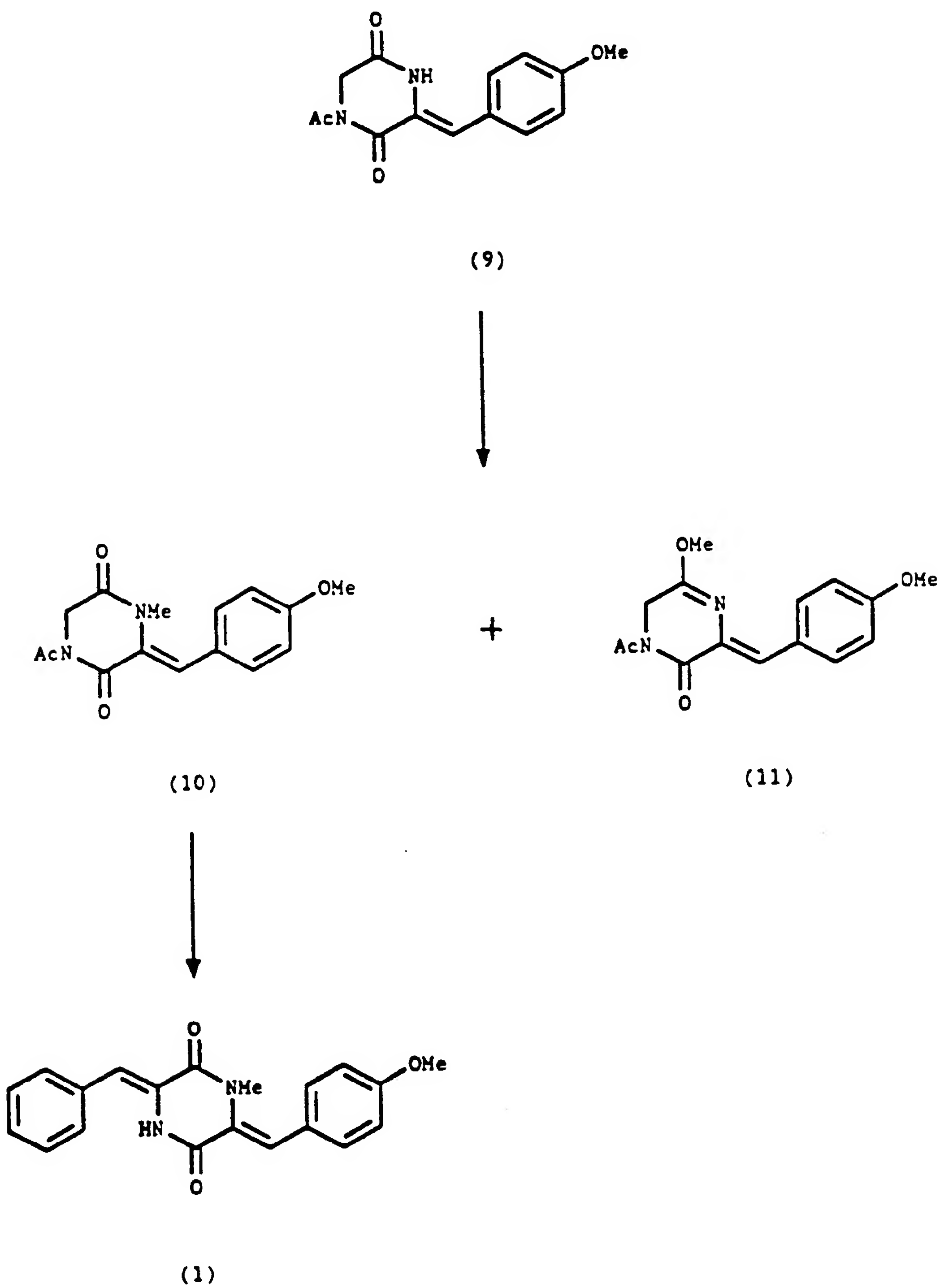
(15) R_1 = H

(10) R_1 = Ac

Compound 12 is treated with NH_3 to afford 3-(4-methoxybenzylidene-2,5-piperazinedione (13). This is then treated with acetic anhydride to yield (3Z)-1-acetyl-3-(4-methoxybenzylidene-2,5-piperazinedione (9).

Compound 12 is treated with, as methylating agent, iodomethane in the presence of potassium carbonate in dimethylformamide to give compound 14. Compound 14 is then treated with NH_3 and subsequently with acetic anhydride to yield 1-acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10).

EXAMPLE 1: Preparation of (3Z,6Z)-3-benzylidene-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione (1) (Scheme 4)



(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10) and 1-Acetyl-5-methoxy-3-(4-methoxybenzylidene)-3,6-dihydropyrazin-2-one (11)

A mixture of (3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) (2.0g, 7.3 mmol), methyl iodide (0.46 ml, 7.3 mmol), and sodium carbonate (800 mg, 7.5 mmol) in dry DMF (50 ml) was stirred under an atmosphere of dry nitrogen for 3 days. The reaction mixture was then poured into ethyl acetate (500 ml) and washed with water (4x100 ml) and brine. The organic phase was separated, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, EtOAc:Hexane, 1:1) to give (3Z)-1-acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10) 1.38 g (66%) as a yellow solid and 1-acetyl-5-methoxy-3-(4-methoxybenzylidene)-3,6-dihydropyrazin-2-one (11) 248 mg (11.8%) as a bright yellow solid.

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10):

$C_{15}H_{16}N_2O_4$

^1H nmr (400 MHz $CDCl_3$):

δ: 2.63 (3H, s, Ac); 2.95 (3H, s, N-Me); 3.87 (3H, s, O-Me); 4.52 (s, 2H, N-CH_2-CO); 6.93 (2H, d, J=8Hz, Aromatic); 7.26 (1H, s, C=CH); 7.29 (2H, d, J=8Hz), Aromatic).

ms (desorption chemical ionisation, ammonia):

m/z (% relative intensity): 306 (34%) MNH_4^+; 289 (100%); 216 (14%)

ir : KBr (diffuse reflectance) ν_{max} (cm^{-1}): 1690, 1700, 3000.

Elemental analysis:

Calculated for $C_{15}H_{16}N_2O_4$: C 62.49, H 5.59, N 9.72

C 62.48, H 5.58, N 9.68.

C 62.51, H 5.65, N 9.67%

1-Acetyl-5-methoxy-3-(4-methoxybenzylidene)-3,6-

dihydropyrazin-2-one (11):

$C_{15}H_{16}N_2O_4$

^1H nmr (400 MHz $CDCl_3$):

δ: 2.68 (3H, s, Ac); 3.86 (3H, s, Ar-OMe); 3.99 (3H, s, O-Me); 4.44 (s, 2H, N-CH_2-CO); 6.95 (2H, d, J=8Hz, Ar); 7.32 (1H, s, C=CH); 8.03 (2H, d, J=8Hz, Ar).

ms (desorption chemical ionisation, ammonia):

m/z (% relative intensity): 289 (100%) MH^+; 247 (14%)

ir : KBr (diffuse reflectance):

ν_{max} (cm^{-1}): 1610, 1690, 1700, 1740, 2950.

Elemental Analysis:

Calculated for $C_{15}H_{16}N_2O_4$:	C 62.49, H 5.59, N 9.72.
	C 62.52, H 5.59, N 9.64.
	C 62.52, H 5.64, N 9.66%

<u>(3Z,6Z)-3-Benzylidene-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione</u> (1)

A mixture of

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (10) (200 mg, 0.69 mmol) and sodium hydride (60% dispersion in oil, 28 mg, 0.69 mmol) in dry DMF (10 ml) was stirred at room temperature for 18 h. Benzaldehyde (71μl, 0.69 mmol) was then added and the reaction mixture stirred at room temperature for 18h. It was then diluted with ethyl acetate (100 ml) and washed with brine (4 x 50 ml). The organic phase was separated, dried ($MgSO_4$), and the solvent removed <u>in vacuo</u>. The residue was purified by flash chromatography (silica, dichloromethane containing 1% MeOH) to give 48 mg (21%) of a yellow solid.

$C_{20}H_{18}N_2O_3$

^1H nmr (400 MHz $CDCl_3$):

δ: 3.06 (3H, s, N-Me); 3.87 (3H, s, O-Me); 6.93 (2H, d, J=8Hz, 2xC-H on Ar-OMe); 7.06 (1H, s, Ph-CH=C); 7.23 (2H, d, J=8Hz, 2xC-H on Ar-OMe); 7.27 (1H, s, MeOAr-C<u>H</u>=C); 7.30-7.48 (5H, m, Ph); (1H, br.s, N-H).

^{13}C nmr (100 MHz $CDCl_3$)

δ: 36.62; 55.34; 113.86; 116.80; 121.30; 126.02; 126.14;

128.47; 128.78; 129.06; 129.45; 131.11; 133.07; 159.66; 159.68; 159.95.

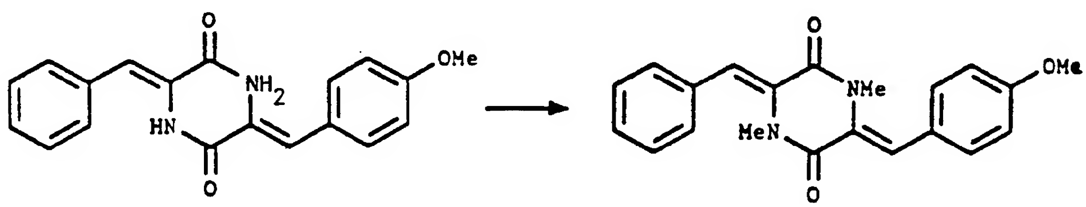
ms (desorption chemical ionisation, ammonia) : 335 (100%) MH^+.

ir : KBr (diffuse reflectance) : ν_{max} (cm^{-1}) : 1690, 3000, 3180, 3400.

Elemental analysis:

Calculated for $C_{20}H_{18}H_2O_3$:	O 71.84, H 5.43, N 8.38.
	C 71.81, H 5.31, N 8.31.
	C 71.80, H 5.25, N 8.31%.

EXAMPLE 2: Preparation of (3Z,6Z)-3-benzylidene-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (2) (Scheme 5)



(1) R_2 = Me (2)

(3) R_2 = H

(3Z,6Z)-3-Benzylidene-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione (2)

A mixture of (3Z,6Z)-3-Benzylidene-6-(4-methoxybenzylidene)-2,5-piperazinedione (3) (0.5 g, 1.56 mmol), sodium hydride (60% dispersion in mineral oil, 125 mg, 3.1 mmol) and methyl iodide (243 µl, 3.9 mmol) in dry DMF (50 ml) was stirred at room temperature for 4 days. The solvent was then removed *in vacuo* and the residue purified by flash chromatography (silica, eluting with EtOAc:Hexane, 1:3) to give 220 mg (40%) of compound 2 as a yellow solid.

$C_{21}H_{20}N_2O_3$

^1H nmr (400 MHz $CDCl_3$)

δ: 2.95 (3H, s, N-Me); 3.04 (3H, s, N-Me); 3.85 (3H, s, O-Me); 6.90 (2H, d, J=8Hz, 2xC-H on Ar-OMe); 7.19 (1H, s, CH=C); 7.21 (1H, s, CH=C) 7.30-7.56 (7H, m, Ph and 2xC-H on Ar-OMe).

ms (desorption chemical ionisation, ammonia) :

m/z (% relative intensity): 349 (100) MH^+.

Example 3: Preparation of Compound 146

Compound 54 (1 equivalent), prepared as in reference Example 5, was treated with sodium hydride (2.0-3.5 equivalents) in DMF at 0°C for 10-90 minutes. The resulting solution was reacted with methyl iodide (2.0-5.0 equivalents) in DMF at room temperature for 3-48 hours. The solvent was then removed _in vacuo_ and the residue purified by flash chromatography to give compound 146 in 49% yield.

By an analogous process other compounds of formula A were prepared by replacing starting compound 54 by the appropriate N-unsubstituted 1,3-dibenzylidene -2,5-piperazinedione bearing the desired substitution pattern in the aromatic ring of one of the benzylidene groups, for instance any of the compounds prepared in the Reference Examples. The following compounds were prepared in this way.

Compound	Yield (%)	Compound	Yield (%)
139	31	141	50
142	50	149	41
144	41	149	51
147	94	149	42
150	43	151	54
153	26	154	71
155	42	156	42
157	24	159	

160	13	161	13

By methylating (3Z,6Z)-6-(2,6-dichlorobenzylidene)-3-(2-nitrobenzylidene)-2,5-piperazinedione under analogous conditions compound 165 was obtained in 23% yield. Compound 153 was prepared from compound 34.

Characterising data for the prepared compounds are provided in Example 16.

Example 4: **Preparation of compound 162**

Compound 69 (1 equivalent), prepared as in Reference Example 7, was treated with sodium hydride (2.0-3.5 equivalents) in DMF at 0°C for 10-90 minutes. The resulting solution was reacted with methyl iodide (2.0-5.0 equivalents) in DMF at room temperature for 3-48 hours. The solvent was them removed _in vacuo_ and the residue purified by flash chromatography to give compound 162 in 13% yield. By an analogous process compounds 163 and 164 were prepared.

Compound	Yield (%)
163	9
164	20

Characterising data for the compounds are set out in Example 16.

Example 5: **Preparation of compound 131**

1-Acetyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione (1 equivalent), compound 10 described in Example 1, was treated with 4-acetamidobenzaldehyde (1 equivalent), and Cs_2CO_3 (1.0-1.1 equivalents) in dimethylformamide at 80°C-100°C for 2-5 hours. Compound 131 was obtained in 48% yield.

By an analogous process other compounds of formula

(A) were prepared by replacing 4-acetamidobenzaldehyde by the appropriately substituted benzaldehyde which will lead to the desired substitution pattern in ring a of the final product. The following compounds were prepared in this way.

Compound	Yield (%)
132	56
133	34
134	67

Characterising data for the compounds are set out in Example 16.

Example 6: Preparation of compounds 121, 122 and 170

1-Acetyl-3-benzylidene-2,5-piperazinedione (compound 18 prepared in Reference Example 2) was N-methylated by treatment with methyl iodide (2.0 equivalents) in the presence of Na_2CO_3 (1.0 equivalents) in DMF at room temperature for 24 hours. The solvent was removed and the residue purified by flash chromatography. The product 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione, obtained in 45% yield, was treated with 4-methoxybenzaldehyde (1.0-1.1 equivalents) in the presence of Cs_2CO_3 in DMF at 80°C for 206 hours to give compound 121 in 35% yield.

By an analogous method, but using benzaldehyde in place of 4-methoxybenzaldehyde, compound 122 was obtained in 68% yield.

Compound 121 prepared as described above was treated with sodium hydride (1.1 equivalents) and bromomethylcyclopropane (1.0 equivalents) in DMF at room temperature for 4 days to give compound 170 in 9% yield.

Characterising data are provided in Example 16.

Example 7: Preparation of Compounds 124, 125, 128 and 130

4-((3Z)-1-acetyl-2,5-dioxopiperazin-3-

ylidene)methylbenzoic acid, methyl ester (1 equivalent) was alkylated at the nitrogen at position 4 of the piperazine ring by treatment with methyl iodide (2.0 equivalents) in the presence of Na_2CO_3 in DMF for 48 hours. The solvent was removed and the residue purified by flash chromatography. The resulting compound (1 equivalent), obtained in 51% yield, was treated with benzaldehyde (1.0 equivalents) in DMF in the presence of Cs_2CO_3 (1.1 equivalents) at 90°C for 2-5 hours to give compound 124 in 54% yield.

By hydrolysing compound 124 with aqueous NaOH in methanol and tetrahydrofuran at room temperature for 5 hours, compound 125 was obtained in 79% yield.

Compound 125 (1 equivalent) was treated with EtOCOCl (1 equivalent) and triethylamine (1 equivalent) in CH_2Cl_2 at 0°C for 30 minutes. Treatment of the resultant solution with ammonia then gave compound 130 in 82% yield. Alternatively, treatment with pyrrolidine (1.0 equivalents) gave compound 128 in 39% yield.

Characterising data for the compounds are provided in Example 16.

Example 8: Preparation of compounds 127, 129, 137, 152 and 171

1-acetyl-3-(4-nitrobenzylidene)-2,5-piperazinedione was N-methylated at position 4 by treatment with methyl iodide (2 equivalents) in the presence of Na_2CO_3 (1 equivalent) in DMF at room temperature for 30 hours. The resulting N-methylated compound was obtained in 34% yield.

(i) Preparation of compounds 127 and 129.

The N-methylated compound was treated with benzaldehyde (1 equivalent) in DMF in the presence of Cs_2CO_3 (1 equivalent) at 80°C for 4 hours to give compound 127 in 67% yield. Compound 127 was reduced by hydrogenation at atmospheric pressure over 10% palladium on carbon as catalyst in CH_2Cl_2 in the presence of a few drops of trifluoroacetic acid at room temperature for 16 hours to

give compound 129 in 17% yield.

(ii) Preparation of compounds 171, 152 and 137

The N-methylated compound was treated with 4-methoxybenzaldelyde (1 equivalent) in DMF in the presence of $Cs_2 CO_3$ (1 equivalent) at 80°C for 4 hours to give compound 171 in 38% yield. Compound 171 was reduced by hydrogenation at atmospheric pressure over 10% palladium on carbon as catalyst in $CH_2 Cl_2$ in the presence of a few drops of trifluoroacetic acid at room temperature for 16 hours to give compound 152 in 95% yield. Compound 152 was acetylated by treatment with acetic anhydride in the presence of triethylamine and DMAP to give compound 137 in low yield.

Example 9: Preparation of compounds 135 and 136

1-Acetyl-3-(2-nitrobenzylidene)-2,5-piperazinedione was N-methylated at position 4 in 31% yield by treatment with sodium hydride (1.1 equivalents) in THF at 0°C for 60 minutes and then with methyl iodide (5.0 equivalents) at room temperature for 18 hours. Subsequent treatment with 4-methoxybenzaldehyde (1 equivalent) in DMF in the presence of Cs_2CO_3 at 90°C for 2 hours gave compound 136 in 32% yield.

By an analogous process starting from 1-acetyl-3-(2,6-dichlorobenzylidene)-2,5-piperazinedione compound 135 was obtained. The yields were 26% for the initial N-methylation and 47% for the subsequent condensation with aldehyde.

Example 10: Preparation of compounds 166 and 167

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione was treated with bromomethylcyclopropane (1 equivalent) in DMF in the presence of Na_2CO_3 (1 equivalent) at 50°C for 48 hours. The product obtained in 11% yield, was condensed with benzaldehyde (1.0 equivalents) in DMF in the presence of Cs_2CO_3 (1.1 equivalents) at 90°C for 2-5 hours to give compound 167 in 30% yield.

Similarly, compound 166 was prepared in 29% yield by treating 1-acetyl-3-benzylidene-2,5-piperazinedione with bromomethylcyclopropane (1.04 equivalents) in DMF in the presence of Na_2CO_3 (1.1 equivalents) at 80-85°C for 5 hours. The product was obtained in 12% yield. It was then condensed with 4-methoxybenzaldehyde (1.2 equivalents) in DMF in the presence of Cs_2CO_3 (1.1 equivalents) at 80°C for 2 hours to give compound 166 in 29% yield.

Example 11: **Preparation of compound 148**

(3Z,6Z)-3-(4-acetoxymethylbenzylidene)-6-benzylidene-2,5-piperazinedione was treated with sodium hydride (2.0-3.5 equivalents) in DMF at 0°C for 10-90 minutes followed by methyl iodide (2.0-5.0 equivalents) in DMF at room temperature for 3-48 hours. Removal of solvent in vacuo and flash chromatography of the residue gave compound 148 in 32% yield and the corresponding compound wherein R_{11}=R_{12}=Me, R_7=CH_2OH R_1-R_6 and R_8-R_{10}=H in 30% yield.

Example 12: **Preparation of compounds 140 and 158**

(3Z,6Z)-3-Benzylidene-6-(1-naphthylmethylene-2,5-piperazinedione, which may be prepared by treating 1-acetyl-3-benzylidene-2,5-piperazinedione with 1-naphthaldehyde (1 equivalent) in DMF in the presence of Cs_2CO_3 (1.0-1.1 equivalents) at 80-100°C for 1 to 6 hours, was methylated by treatment with NaH (2.0-3.5 equivalents) in DMF at 0°C for 10-90 minutes followed by methyl iodide in DMF at room temperature for 3-48 hours. Removal of solvent in vacuo and flash chromatography of the residue gave compound 140 in 51% yield.

By an analogous method, compound 158 was prepared by methylation of (3Z,6Z)-3-benzylidene-6-(2-N-methyltrimethylacetamidobenzylidene)-2,5-piperazinedione in 49% yield.

Example 13: **Interconversions of compounds A**

(i) Compound (1) prepared as described in Example 1 was

treated with BBr_3 (10.0 equivalents) in CH_2Cl_2 at room temperature for 2-5 hours to give compound 123 in 45% yield.

(ii) Compound 122 was treated with sodium hydride, then ethyl iodide (1 equivalent) in DMF at room temperature overnight. The solvent was removed in vacuo and the residue purified by flash chromatography to give compound 169 in 40% yield.

(iii) Compound (1) was treated with bromomethylcyclopropane (1.5 equivalents) in DMF in the presence of Na_2CO_3 (1.0 equivalents) at 85°C for 4 hours to give compound 168 in 11% yield.

Example 14 **Pharmaceutical composition**

Tablets, each weighing 0.15 g and containing 25 mg of a compound of the invention can be manufactured as follows: Composition for 10,000 tablets

compound of the invention (250 g)
lactose (800 g)
corn starch (415 g)
talc powder (30 g)
magnesium stearate (5 g)

The compound of the invention, lactose and half of the corn starch are mixed. The mixture is then forced through a sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml). The resulting paste is used to granulate the powder. The granulate is dried and broken up into small fragments on a sieve of 1.4 mm mesh size. The remaining quantity of starch, talc and magnesium stearate is added, carefully mixed and processed into tablets.

Example 15: **Testing of compounds A as modulators of MDR**

Materials and Methods

The EMT6 mouse mammary carcinoma cell line and the MDR resistant subline AR 1.0 were cultured in RPMI 1640

medium containing 10% foetal calf serum and 2mM glutamine at 37°C in 5% CO_2. Cells were passaged between 1 in 200 and 1 in 2000 in the case of the parental cell line and between 1 in 20 and 1 in 200 in the case of the MDR resistant subline, after trypsinisation (0.25% trypsin, $0.2gl^{-1}$, EDTA).

1. Drug accumulation assay

AR 1.0 cells were seeded into 96 well opaque culture plates (Canberra Packard). The assay medium contained a mixture of tritiated Daunorubicin (DNR), a cytotoxic agent, and unlabelled DNR (0.25 μ Ci/ml; 2μM). Compounds of formula A were serially diluted in assay medium over a range of concentrations from 100 nM to 100 μM. The cells were incubated at 37°C for 1 hr before washing and counting of cell associated radioactivity. Each assay included a titration of the known resistance modifying agent Verapamil as positive control. Results were expressed as % maximum accumulation where 100% accumulation is that observed in the presence of 100μM Verapamil.

The results are set out in the following Table 3.

TABLE 3

Compound No.	Accumulation IC_{50}(μM) or % max		Compound No.	Accumulation IC_{50}(μM) or % max
1	20 μM			
121	80 μM		122	100 μM
124	32% max		126	45% max
131	50 μM		132	8 μM
133	39% max		134	50% max
135	15 μM		136	36%
137	44% max		138	100 μM
139	30 μM		140	10 μM
140	10 μM		141	25 μM
142	40 μM		143	45% max
144	25 μM		145	35 μM
146	35 μM		147	40 μM
148	65 μM		149	30 μM
150	50 μM		151	20 μM
153	80 μM		154	30 μM
155	20 μM		156	30% max
157	30 μM		158	20 μM
159	15% max		160	35 μM
161	20 μM		162	15 μM
163	20 μM		164	20 μM
165	7 μM		166	10 μM
167	10 μM		168	12 μM
169	25 μM		170	10 μM

2. Potentiation of Doxorubicin toxicity

Compounds of formula A were examined for their ability to potentiate the toxicity of doxorubicin in AR 1.0 cells. In initial proliferation assays compounds were titrated against a fixed concentration of doxorubicin (0.5-1μM) which alone is non-toxic to AR 1.0 cells. Incubations with doxorubicin were over a four day period before

quantitation of proliferation using the colorimetric sulphorhodamine B assay (Skehan et al; J. Natl. Cancer Inst. 82 pp 1107-1112 (1990))

Compounds which were shown to be able to sensitise AR 1.0 cells to 0.8-1.7 μM doxorubicin without high innate toxicity were selected for further study. Cells were cultured for four days with concentrations of doxorubicin over the range of 0.5 nM-50 μM in the presence of Verapramil at its maximum subtoxic level determined from previous experiments. Proliferation was quantified as described by Skehan et al, loc cit. The IC_{50} (concentration required to reduce proliferation to 50% of the untreated controls) for doxorubicin alone and with the Verapamil were derived and used to calculate the potentiation index (PI):

$$PI = \frac{IC_{50} \text{ for Doxorubicin alone}}{IC_{50} \text{ for Doxorubicin plus RMA}}$$

TABLE 4

Compound	Potentiation Index
164	7.5 (at 3μM)
166	10 (at 3 μM)
166	10 (at 5 μM)
167	6 (at 3 μM)
168	20 (at 3 μM)

Example 16: Characterization of compounds of formula A

The compounds prepared in Examples 1 to 13 were characterised by conventional mass spectroscopic, microanalytical, proton nmr and i.r. techniques. The results are set out in Table 5.

TABLE 5

Nº	Mol. Formula (M. Wt)	Mass spec m/z, intensity (mode)	^{1}Hnmr Solvent δ All 400 MHz	Microanalysis	Calc	Found		Infra-red
121	$C_{20}H_{18}N_2O_3$ = 334	335, MH^+, 100% 276 (10%), 259 (20%), 217 (20%), 154 (20%). (DCI/NH_3)	d_6-DMSO 10.38 (s,1H), 7.55 (d,2H), 7.45-7.32 (m,5H), 7.07 (s,1H), 7.00 (d,2H), 6.80 (s,1H), 3.80 (s,3H), 2.85 (s,3H).	C H N	71.84 5.43 8.38	70.91 5.18 8.36	71.10 5.37 8.37	3200, 3020, 2820, 1690, 1600, 1530.
122	$C_{19}H_{16}O_2N_2$ = 304	305, M^+H, 100% (DCI/NH_3)	$CDCl_3$ 3.00 (3H,s), 7.07 (1H,s), 7.28 (11H,M), 7.99 (1H,Broad singlet).	C H N	74.98 5.30 9.20	74.54 5.24 9.12		
123	$C_{19}H_{16}N_2O_3$ = 320	320, M^+, 100% (EI^+)	$CDCl_3+CF_3CO_2D$ 3.14 (3H,s) 6.90 (2H,d, J=8Hz), 7.28 (2H,d, J=8Hz), 7.35 - 7.50 (7H,m).	C H N	71.24 5.03 8.74	70.62 4.97 8.56	70.62 4.99 8.57	

124	$C_{21}H_{18}N_2O_4$	380, MNH_4^+, 7% 363, MH^+, 363 100% DCI/NH_3	$CDCl_3$ 3.00 (3H,s), 3.91 (3H,s), 7.10 (1H,s), 7.29 (1H,s), 7.34 (2H,d, J=6HZ), 7.35 - 7.49 (5H,m), 8.04 (2H,d, J=6Hz).	C H N	69.60 5.01 7.73	68.84 5.03 7.64	68.70 5.01 7.64	
125	$C_{20}H_{16}N_2O_4$	366, MNH4$^+$, 1% 349 (MH^+, 100%), 279 (17%) DCI/NH_3	d_6-DMSO 2.86 (3H,s), 6.85 (1H,s), 7.09 (1H,s), 7.32 (1H,m), 7.38-7.50 (4H,m), 7.58 (2H,d, J=7Hz), 7.95 (2H, J=7Hz), 8.53 (1H, br.s).	C H N	68.96 4.63 8.04	68.54 4.65 7.81	68.65 4.71 7.99	
126	$C_{21}H_{20}N_2O_3$	366, MNH_4^+, 2% 349, MH^+, 100%	$CDCl_3$ 3.00 (6H,s) 4.78 (2H,s) 7.25 (2H,s) 7.45 (9H,s)					
127	$C_{19}H_{15}N_3O_4$ = 349	350, MH^+, 100% 367, MNH_4^+, 10% 320 (10%) DCI/NH_3	$CDCl_3$, 8.25 (d,2H), 8.11 (s,1H), 7.49-7.38 (m,7H), 7.28 (s,1H), 7.11 (s,1H), 3.01 (s,3H).	C H N	65.32 4.33 12.03	65.03 4.28 11.87	65.31 4.25 11.94	

128	$C_{24}H_{23}N_3O_3$	419, MNH_4^+, 1% 402, MH+, 100% DCI/NH_3	$CDCl_3$ 1.85-2.05 (4H,m), 3.00 (3H,s), 3.46 (2H,m), 3.68 (2H,m), 7.09 (1H,s), 7.29 (1H,s), 7.30 (2H,d, J=8Hz), 7.32-7.52 (5H,m), 7.58 (2H,d, J=8Hz), 8.01 (1H,br.s).					
129	$C_{19}H_{17}N_3O_2$ = 319	320, MH^+, 100% DCI/NH_3	$CDCl_3$ 7.93(s,1H), 7.48 - 7.42 (m,5H), 7.21 (s,1H), 7.12 (d,2H), 7.05 (s,1H), 6.68 (d,2H), 3.08 (s,3H).					
130	$C_{20}H_{17}N_3O_3$ = 319	365, MNH_4^+, 11% 348, MH^+, 100% DCI/NH_3	d_6-DMSO 2.85 (3H,s), 6.86 (1H,s), 7.09 (1H,s), 7.24-7.49 (6H,m), 7.52 (2H,d, J=6Hz), 7.87-8.01 (3H,m), 10.50 (1H,br.s)	C H N	69.15 4.93 12.10	68.47 4.96 11.57	68.53 4.95 11.59	

131	$C_{22}H_{21}N_3O_4$ = 391	409, MNH_4^+, 28% 392, MH^+, 100% DCI/NH_3	$CDCl_3$+CF_3CO_2H 2.32 (3H,s), 3.11 (3H,s), 3.89 (3H,s), 6.96 (2H,d), 7.19 (1H,s), 7.28 (2H,d), 7.40 (1H,s), 7.48 (2H,d), 7.59 (2H,d).					
132	$C_{20}H_{16}N_2O_3Cl_2$ = 402	403/405/407, (100/64/13) %	$CDCl_3$ 3.06 (3H, s), 3.84 (3H, s), 6.90-6.93 (3H, m), 7.23-7.28 (4H, m), 7.40 (2H, d)	C H N Cl	59.57 4.00 6.95 17.58	59.37 4.11 7.01 16.95	59.48 4.11 7.05 16.95	
133	$C_{20}H_{17}N_3O_5$ = 379	380, 100% 397, 76%	$CDCl_3$ 3.06 (3H, s), 3.87 (3H, s), 6.44 (2H, d), 7.18 (1H, s), 7.23-7.28 (2H, m) 7.32 (1H, s), 7.51-7.59 (2H, m), 7.73 (1H, t), 8.01 (1H, bs), 8.20 (1H, d)					

134	$C_{23}H_{23}N_3O_4$ = 405	423, MNH_4^+, 60% 406, MH^+, 100% DCI/NH_3	$CDCl_3$+CF_3CO_2H 2.32(3H,s), 3.06 (3H,s), 3.3 (3H,s), 3.86 (3H,s), 6.92 (2H,d), 7.02 (1H,s), 7.22-7.39 (6H,m), 7.49 (2H,d)					
135	$C_{20}H_{16}N_2O_3Cl_2$ = 402	403, 405, 407 (93, 100, 46)% 367, 369, 371, 373 (29, 59, 51, 39)% DCI/NH_3	$CDCl_3$ 2.89 (3H, s), 3.87 (3H, s), 6.98 (2H, d), 7.04 (1H, s), 7.07 (1H, s), 7.21-7.26 (1H, m), 7.36 (4H, m), 8.06 (1H, very broad s)	C H N	59.57 4.00 6.95	59.03 3.95 6.94	59.01 3.88 7.01	
136	$C_{20}H_{17}O_5N_3$ = 379	397, 16% 380, 100% 333, 49% DCI/NH_3	$CDCl_3$ 2.90 (3H, s), 3.86 (3H, s), 6.99 (2H, d), 7.06 (1H, s), 7.30-7.40 (3H, m), 7.45 (1H, s), 7.53 (1H, t), 7.66 (1H, t), 8.07 (1H, very broad s), 8.19 (1H, d)	C H N	63.32 4.52 11.08	63.06 4.46 10.70	62.95 4.47 10.76	

137	$C_{22}H_{21}N_3O_4$ = 391	392, MH^+, 100% 409, MNH_4^+, 10% DCI/NH_3	d_6-DMSO 10.28 (s,1H), 10.00 (s,1H), 7.61 (d,2H), 7.55 (d,2H), 7.28 (d,2H), 7.00 - 7.03 (m,3H), 6.76 (s,1H), 3.78 (s,3H), 2.88 (s,3H), 2.05 (s,3H).					
138	$C_{25}H_{30}N_5O_4Cl$	472, MH^+, 1% 436, MH^+-HCl, 100%	$CDCl_3$ 2.46 (2H,m), 2.88 (6H,d, J=3Hz), 3.05 (3H,s), 3.27 (2H,m), 3.88 (3H,s), 4.16 (2H,m), 6.90-7.01 (5H,m), 7.20-7.28 (2H,m), 7.36 (2H,d, J=7Hz), 7.90 (1H,br.s), 12.90 (1H,br.s). (under $CDCl_3$ peak)					

Nº	Mol. Formula (M. Wt)	Mass spec m/z, intensity (mode)	^{1}Hnmr Solvent δ All 400 MHz	Microanalysis Calc		Found		Infra-red
139	$C_{21}H_{17}N_2O_2F_3$ = 386	387, MH^+, 100% 319 (<10%) DCI/NH_3	$CDCl_3$ 7.65 (d,2H), 7.47 (d,2H), 7.45-7.33 (m,6H), 7.22 (s,1H), 2.99 (s,3H), 2.97 (s,3H).	C H N	65.28 4.43 7.25	65.46 4.56 7.10	65.44 4.59 7.12	
140	$C_{24}H_{20}N_2O_2$ = 368	368, M^+, 20% 369, MH^+, 100% DCI/NH_3	$CDCl_3$ 8.05 (d,1H), 7.91-7.84 (m,2H), 7.73 (s,1H), 7.61-7.32 (m,9H), 7.30 (s,1H), 3.03 (s,3H), 2.77 (s,3H).					
141	$C_{22}H_{23}N_3O_2$ = 361	362, MH^+, 100% 257, 55% DCI/NH_3	$CDCl_3$ 7.37-7.30 (m,5H), 7.26 (s,1H), 7.23 (s,1H), 7.18 (d,2H), 6.71 (d,2H), 3.07 (s,3H), 3.02 (s,6H), 2.96 (s,3H).					

142	$C_{21}H_{20}N_2O_3$ = 348	349, MH^+, 100% 366, MNH_4^+, 5% 317(15%) DCI/NH_3	$CDCl_3$ 7.41-7.31 (m,6H), 7.30 (s,1H), 7.23 (s,1H), 7.20 (m,1H), 7.0 - 6.9 (m,2H), 3.85 (s,3H), 2.99 (s,3H), 2.92 (s,3H).					
143	$C_{20}H_{19}N_3O_2$ = 333	334, MH^+, 100% 318 (20%), 290 (30%), 277 (20%). DCI/NH_3	$CDCl_3$ 7.39-7.30 (m,SH), 7.19 (s,1H), 7.17 (d,2H), 7.14 (s,1H), 6.68 (d,2H), 3.05 (s,3H), 2.95 (3H), 2.90 (s,b,2H).					
144	$C_{12}H_{17}N_2O_2F$ = 336	337 100% DCI/NH_3	$CDCl_3$ 2.98 (3H, s), 3.00 (3H, s), 7.10-7.44 (11H, m)					
145	$C_{20}H_{17}N_2O_2F$ = 336	337 100% DCI/NH_3	$CDCl_3$ 2.98 (6H, overlapping singlets), 7.10 (2H, t), 7.18 (1H, s), 7.25 (1H, s), 7.30-7.42 (9H, m)					

146	$C_{20}H_{16}N_2O_2F_2$		$CDCl_3$ 2.96 (3H, s), 2.99 (3H, s), 6.85-6.97 (2H, m), 7.11 (1H, s), 7.24 (1H, s), 7.30-7.41 (6H, m)	C H N	67.79 4.55 7.91	67.66 4.56 7.84	67.67 4.56 7.83	
147	$C_{23}H_{22}N_2O_4$	391, M^+H, 8% 363 (100%) DCI/NH_3	$CDCl_3$ 7.41-7.28 (8H,m), 7.23 (2H,d), 4.48 (2H,s), 3.42 (3H,s), 2.98 (6H,s).					
148	$C_{21}H_{20}N_2O_3$ = 348	349, MH^+ 366, MNH_4^+, 2% DCI/NH_3	$CDCl_3$ 7.45 (9H,m), 7.25 (2H,s), 4.78 (2H,s), 3.00 (6H,s).					
149	$C_{22}H_{22}N_2O_3$ = 362	363, MH^+, 100% DCI/NH_3	$CDCl_3$ 7.41-7.28 (m,7H), 7.20 (s,1H), 7.18 (S,1H), 6.92 (d,2H), 4.08 (q,2H), 3.02 (s,3H), 2.96 (s,3H), 1.42 (t,3H).	C H N	72.91 6.12 7.73	72.42 6.03 7.59	72.56 6.13 7.63	

150	$C_{20}H_{18}N_2O_2$ = 318	319, MH^+, 100% DCI/NH_3	$CDCl_3$ 7.41-7.31 (m,10H), 7.24 (s,2H), 2.99 (s,6H).					
151	$C_{20}H_{16}N_2O_2Cl_2$ = 387	387, MH^+, 100% 389 (60%), 391 (10%), MNH_4^+ 404 (<10%), 351, 353, 355; 338; 324; 310 DCI/NH_3	$CDCl_3$ 7.41-7.30 (m,7H), 7.28 (s,1H), 7.26 (m,1H), 7.05 (s,1H), 2.99 (s,3H), 2.78 (s,3H).	C H N	62.03 4.16 7.23	61.89 4.11 7.09	61.95 4.10 7.10	
152	$C_{20}H_{19}N_3O_3$	350, MH^+, 100%	$CDCl_3$ 3.08 (s,3H) 3.83 (s,3H) 6.68 (d,2H) 6.95-7.00 (m,3H) 7.13 (d,2H) 7.20 (s,1H) 7.38 (d,2H) 7.85 (s,1H)					
153	$C_{23}H_{23}N_3O_3$ = 389	390, MH^+, 100% 407, MNH_4^+, 10% 389 (60%), 391 (20%), 347 (10%) DCI/NH_3	$CDCl_3$ 7.40-7.30 (m, 7H), 7.26-7.20 (m,4H), 3.29 (s,3H), 2.99 (s,3H), 1.95 (s,broad,3H).	C H N	70.93 5.95 10.79	70.82 5.97 10.76	70.71 5.95 10.74	

154	$C_{20}H_{16}N_2O_2Cl_2$	404, 406, 408, $(M+NH_4)^+$, 2% 387, 389, 391, $(M+H)^+$, 100%	$CDCl_3$, 7.45 (1H,d), 7.42-7.28 (6H,m), 7.15 (2H,dd), 7.09 (1H,s), 2.99 (3H,s), 2.97 (3H,s).					
155	$C_{20}H_{17}N_2O_2Cl$ = 352.5	353, MH^+, 100% 355 (40%), 319 (10%) DCI/NH_3	$CDCl_3$ 7.41-7.30 (m,8H), 7.27 (s,1H), 7.22 (s,1H), 7.17 (s1H), 2.98 (s,6H)	C H N	68.09 4.86 7.94	67.83 4.96 7.60	67.86 5.00 7.67	
156	$C_{21}H_{20}N_2O_3S$ = 380	381, MH^+, 100% (50%),365 DCI/NH_3	$CDCl_3$ 7.68 (d,2H), 7.50 (d,2H), 7.44-7.31 (m,6H), 7.22 (s,1H), 2.99 (s, 3H), 2.98 (s,3H), 2.77 (s,3H).					

157	$C_{22}H_{23}N_3O_4S$ = 425	426, MH+, 100% 443, MNH_4+, 10% (15%), 412 DCI/NH_3	$CDCl_3$ 7.81 (d,2H), 7.49 (d,2H), 7.41-7.31 (m,5H), 7.28 (s,1H), 7.22 (s,1H), 2.99 (s,3H), 2.97 (s,3H), 2.74 (s,6H)	C H N	62.09 5.45 9.88	61.20 5.54 9.34	61.14 5.50 9.28	
158	$C_{26}H_{29}N_3O_3$ = 431	432, MH+, 100% 330 (10%), 346 (10%)	$CDCl_3$ 7.41-7.30 (m,8H), 7.23 (s,1H), 7.22 (m,1H), 7.11 (s,1H), 3.28 (s,3H), 3.02 (s,3H), 2.97 (s,3H), 1.2 (s,9H).					
159	$C_{26}H_{22}N_2O_2$	395, M^+H, 100% DCI/NH_3	$CDCl_3$ 7.67-7.58 (4H,m), 7.48-7.29 (9H,m), 7.26-7.21 (3H,m), 3.06 (3Hs), 2.98 (3H,s).					

160	$C_{22}H_{20}N_2O_4$	377, $(M+H)^+$, 100% DCI/NH_3	$CDCl_3$ 8.05 (2H,d), 7.42-7.29 (8H,m), 7.22 (1H,s), 2.99 (3H,s), 2.96 (3H,s).					
161	$C_{20}H_{17}N_2O_2Br$ = 397 ± 1	397:399, (1:1), 100% DCI/NH_3	d_6-DMSO 2.86 (6H, two singlets of virtually identical shift), 7.01 (1H, s), 7.08 (1H, s), 7.31-7.45 (7H, m), 7.60 (2H, d)					
162	$C_{21}H_{18}N_2O_3F_2$ = 384	385 100%	$CDCl_3$ 2.97 (3H, s), 3.02 (3H, s), 3.86 (3H, s), 6.85-6.96 (4H, m), 7.09 (1H, s), 7.19 (1H, s), 7.23-7.30 (3H, m)					

163	$C_{21}H_{19}N_2O_3Br$ = 427 ± 1	427:429 100:100% DCI/NH_3	$CDCl_3$ 2.97 (3H, s), 3.02 (3H, s), 3.85 (3H, s), 6.92 (2H, d), 7.12 (1H, s), 7.17 (3H, m), 7.23-7.30 (2H, m) 7.53 (2H, d)	C H N	59.03 4.48 6.56	58.85 4.46 6.46	58.79 4.49 6.47	
164	$C_{21}H_{19}N_2O_3F$ = 366	367 100% DCI/NH_3	$CDCl_3$ 2.98 (3H, s), 3.01 (3H, s), 3.85 (3H, s), 6.93 (2H, d), 7.10 (2H, m), 7.18 (2H, d), 7.26-7.35 (4H, m)	C H N	68.84 5.23 7.65	68.42 5.19 7.55	68.47 5.27 7.54	
165	$C_{20}H_{15}N_3O_4Cl_2$ = 431	449/451/453 (9:6:1) 100% 432/434/436 (9:6:1) 64% 402 24%	$CDCl_3$ 2.81 (3H, s), 2.85 (3H, s), 7.09 (1H, s), 7.23-7.29 (1H, m), 7.33-7.40 (3H, m), 7.47 (1H, s), 7.56 (1H, t), 7.69 (1H, t), 8.17 (1H, d)	C H N	55.57 3.50 9.72	55.34 3.48 9.56	55.36 3.50 9.55	

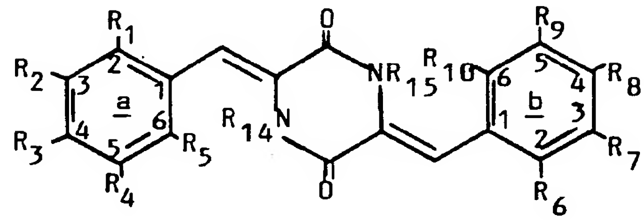
Nº	Mol. Formula (M. Wt)	Mass spec m/z, intensity (mode)	^{1}Hnmr Solvent δ All 400 MHz	Microanalysis	Calc	Found		Infra-red
166	$C_{23}H_{22}N_2O_3$ = 374	375, M^+H, 100% DCI/NH_3	$CDCl_3$ 0.02-0.08 (2H,m), 0.43-0.47 (2H,m), 0.95-1.04 (1H,m), 3.55 (2H,d), 3.85 (3H,s), 6.98 (2H,d), 7.02 (1H,s), 7.22 (1H,s), 7.30-7.40 (7H,m), 7.94 (1H,broad,s).	C H N	73.78 5.92 7.48	73.59 5.77 7.46	73.56 5.90 7.44	

167	$C_{23}H_{22}N_2O_3$	375, MH^+, 100% DCI/NH_3	$CDCl_3$ 0.10 (2H,m), 0.39 (2H,m), 1.05 (1H,m), 3.58 (2H,d, J=6Hz), 3.86 (3H,s), 6.90 (2H,d, J=7Hz), 7.05 (1H,s), 7.20 (1H,s), 7.28 (2H,d, J=7Hz), 7.35 (1H,m), 7.43 (4H,m), 7.87 (1H,br.s)					
168	$C_{24}H_{24}N_2O_3$	389, 100% DCI/NH_3	$CDCl_3$ 0.09 (2H, m), 0.37 (2H, m), 1.00 (1H, m), 3.05 (3H, s), 3.49 (2H, d), 3.35 (3H, s), 6.42 (2H, d), 7.16 (2H, d), 7.27-7.40 (7H, m)					
169	$C_{21}H_{20}N_2O_2$	333, M^+H, 100% DCI/NH_3	$CDCl_3$ 7.42-7.29 (10H,m), 7.19 (2H,d), 3.62 (2H,q), 2.98 (3H,s), 0.99 (3H,t).					

170	$C_{24}H_{24}N_2O_3$	389, MH^+, 100% 333, 305, 257 All <10% DCI/NH_3	7.40-7.30 (m,7H), 7.19 (s,1H), 7.11 (s,1H), 6.92 (d,2H), 3.85 (s,3H), 3.52 (d,2H), 3.00 (s,3H), 1.01 (m,1H), 0.48 (m,2H), 0.09 (m,2H).	C H N	74.21 6.23 7.21	73.95 6.24 7.15	74.20 6.28 7.26	
171	$C_{20}H_{17}N_3O_5$	397, MNH_4^+, 10% 380, MH^+, 100% DCI/NH_3	$CDCl_3$+CF_3CO_2D 3.06 (s,3H) 3.90 (s,3H) 7.03 (d,2H) 7.28 (s,1H) 7.42 (s,1H) 7.45 (d,2H) 7.51 (d,2H) 8.31 (d,2H)					

CLAIMS

1. A diketopiperazine of formula (A):



(A)

wherein each of R_{14} and R_{15}, which may be the same or different, is independently selected from hydrogen and C_1-C_6 alkyl provided at least one of R_{14} and R_{15} is C_1-C_6 alkyl; and each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl or, when R^{11} and R^{12} are attached to the same nitrogen atom, they may alternatively form with the nitrogen atom a saturated five or six-membered heterocyclic ring; and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of R_1 to R_{10} is H; and

(ii) R_{14} and R_{15} are both Me, R_8 is OMe and the rest of R_1 to R_{10} are H.

2. A compound according to claim 1 wherein one of

R_{14} and R_{15} is Me, Et or cyclopropylmethyl and the other is hydrogen, Me, Et or cyclopropylmethyl.

3. A compound according to claim 1 or 2 wherein one of R_6 to R_{10} is selected from hydroxy, halogen, alkoxy, $-NHCOR^{11}$ $-CO_2R^{11}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-NO_2$, $-SO_2N(R^{11}R^{12})$, $-SOR^{13}$, and $-N(R^{11})COR^{12}$ and the other four of R_6 to R_{10} are H.

4. A compound according to claim 3 wherein R^8 is selected from hydroxy, halogen, alkoxy, $-NHCOR^{11}$, $-CO_2R^{11}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-NO_2$, $-SO_2N(R^{11}R^{12})$, $-SOR^{13}$, and $-N(R^{11}COR^{12})$ and R_6, R_7, R_9 and R_{10} are H.

5. A compound according to any one of the preceding claims wherein R_1 is H, halogen or NO_2; R_2 is H; R_3 is H, $-NHCOR^{11}$, $N(R^{11}COR^{12})$, C_1-C_6 alkoxy or halogen; R_4 is H and R_5 is H or halogen.

6. A compound according to any one of claims 1 to 3 wherein any two adjacent groups of R_1 to R_{10} form, together with the carbon atoms to which they are attached, an optionally substituted benzene ring.

7. A compound according to claim 1 selected from:

(3Z,6Z)-3-benzylidene-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;

(3Z,6Z)-6-benzylidene-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;

(3Z,6Z)-3,6-dibenzylidene-1-methyl-2,5-piperazinedione;

(3Z,6Z)-3-benzylidene-6-(4-hydroxybenzylidene)-1-methyl-2,5-piperazinedione;

4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzoic acid, methyl ester;

4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzoic acid;

(3Z,6Z)-3-(3-hydroxymethylbenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione;

(3Z,6Z)-3-benzylidene-1-methyl-6-(4-nitrobenzylidene)-2,5-piperazinedione;

N,N-tetramethylene-4-((3Z,6Z)-3-benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzamide;

(3Z,6Z)-6-(4-aminobenzylidene)-3-benzylidene-1-methyl-2,5-

piperazinedione;
4-((3Z,6Z)-3-Benzylidene-1-methyl-2,5-dioxopiperazin-6-ylidene)methylbenzamide;
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;
(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;
(3Z,6Z)-6-(4-Methoxybenzylidene)-1-methyl-3-(2-nitrobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-(4-Methoxybenzylidene)-1-methyl-3-(4-N-methylacetamidobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-(2,6-Dichlorobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-Methoxybenzylidene)-1-methyl-6-(2-nitrobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-(3-N,N-Dimethylaminopropoxy)benzylidene)-6-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione, hydrochloride;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-trifluoromethylbenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(1-naphthylmethylene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(4-dimethylaminobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(2-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-Aminobenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(2-fluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(4-fluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(2,4-difluorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-Acetoxymethylbenzylidene)-6-benzylidene-1,4-

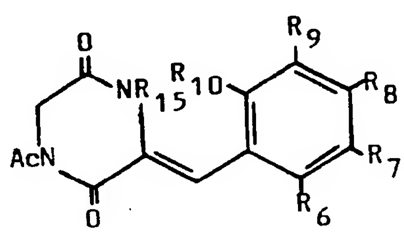
dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(3-Acetoxymethylbenzylidene)-6-benzylidene-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(4-ethoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3,6-Dibenzylidene-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(2,6-dichlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-(4-aminobenzylidene)-3-(4-methoxybenzylidene)-1-methyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-<u>N</u>-methylacetamidobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(3,4-dichlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-3-(3-chlorobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-methylsulfinylbenzylidene)-2,5-piperazinedione;
<u>N</u>,<u>N</u>-Dimethyl-4-((3Z,6Z)-6-Benzylidene-1,4-dimethyl-2,5-dioxopiperazin-3-ylidene)methylbenzenesulfonamide;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(2-<u>N</u>-methyltrimethylacetamidobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1,4-dimethyl-3-(4-phenylbenzylidene)-2,5-piperazinedione;
4-((3Z,6Z)-6-Benzylidene-1,4-dimethyl-2,5-dioxopiperazin-3-ylidene)methylbenzoic acid, methyl ester;
(3Z,6Z)-6-Benzylidene-3-(4-bromobenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(2,4-Difluorobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-Bromobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(4-Fluorobenzylidene)-6-(4-methoxybenzylidene)-1,4-dimethyl-2,5-piperazinedione;
(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-1,4-dimethyl-6-(2-nitrobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1-cyclopropylmethyl-3-(4-

methoxybenzylidene)-2,5-piperazinedione;
(3Z,6Z)-3-Benzylidene-1-cyclopropylmethyl-6-(4-methoxybenzylidene)-2,5-piperazinedione;
(3Z,6Z)-6-Benzylidene-1-cyclopropylmethyl-3-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione;
(3Z,6Z)-3,6-Dibenzylidene-1-ethyl-4-methyl-2,5-piperazinedione;
(3Z,6Z)-3-Benzylidene-1-cyclopropylmethyl-6-(4-methoxybenzylidene)-4-methyl-2,5-piperazinedione

8. A pharmaceutical or veterinary composition comprising a pharmaceutically or veterinarily acceptable carrier or diluent and, as an active principle, a compound as claimed in any one of the preceding claims.

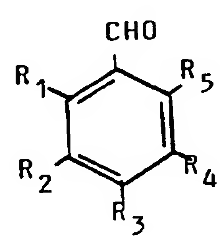
9. A process for preparing a compound as defined in claim 1, the process comprising:

(a) condensing a compound of formula (I):



(I)

wherein R_6 to R_{10} and R_{15} are as defined in claim 1 and are optionally protected, with a compound of formula (II):

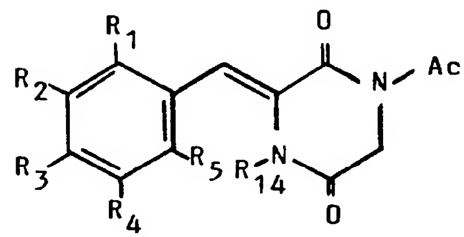


(II)

wherein R_1 to R_5 are as defined in claim 1 and are

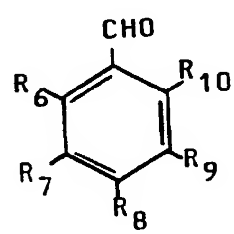
optionally protected, in the presence of a base in an organic solvent thereby obtaining a compound of formula A in which R_{14} is hydrogen; or

(b) condensing a compound of formula (I'):



(I')

wherein R_1 to R_5 and R_{14} are as defined in claim 1 and are optionally protected with a compound of formula (III):



(III)

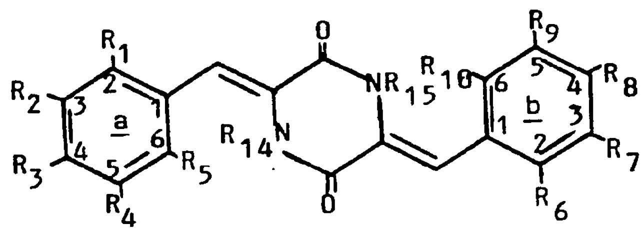
wherein R_6 to R_{10} are as defined in claim 1 and are optionally protected, in the presence of a base in an organic solvent; and

(c) if desired, converting the resulting compound of formula A in which R_{14} or R_{15}, respectively, is hydrogen into a corresponding compound of formula A in which R_{14} or R_{15}, respectively, is a C_1-C_6 alkyl group, by treatment with an alkylating agent; and/or, if required, removing optionally present protecting groups, and/or, if desired, converting one compound of formula A into another compound of formula A, into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or,

if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers into the single isomers.

10. A compound as defined in any one of claims 1 to 8 for use as a modulator of multiple drug resistance.

11. Use of a diketopiperazine of formula (A):



(A)

wherein each of R_{14} and R_{15}, which may be the same or different, is independently selected from hydrogen and C_1-C_6 alkyl provided at least one of R_{14} and R_{15} is C_1-C_6 alkyl; each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl or, when R^{11} and R^{12} are attached to the same nitrogen atom, they may alternatively form with the nitrogen atom a saturated five or six membered heterocyclic ring; and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring

which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; in the manufacture of a medicament for use as a modulator of multiple drug resistance.

12. Use according to claim 11, wherein the compound is a compound as defined in any of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 93/01735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D241/08 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN vol. 59 , 1986 , TOKYO JP pages 3917 - 3923 CHUNG-GI SHIN ET AL. 'CONVENIENT SYNTHESIS OF 3-AMINOCOUMARIN DERIVATIVES BY THE CONDENSATION OF 1,4-DIACETYL-OR 3-SUBSTITUENT-2,5-PIPERAZINDIONES WITH VARIOUS SALICYLALDEHYDE DERIVATIVES.' see page 3919 - page 3921; example 8C --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1993	30. 11. 93
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer FRANCOIS, J

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/GB 93/01735

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 69, no. 28, 1968, Columbus, Ohio, US; abstract no. 96654q, R.F.C. BROWN 'SYNTHETIC APPROACHES OF MYCELIANAMIDE.' page 9051 ; see abstract	1
X	& AUST. J. CHEM. vol. 21, no. 6 , 1968 , CANBERRA pages 1581 - 1599	1

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